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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:
KUSTERS ET AL.

Serial Number: 09/904,994 Group Art Unit: To be assigned

Filed: July 13, 2001 Examiner: To be assigned

For: HELICOBACTER FELIS VACCINE

CLAIM TO PRIORITY UNDER 35 USC 119

Assistant Commissioner of Patents
Washington, D.C. 20231

July 30, 2001

Sir:

The benefit of the filing date of the following prior foreign application is hereby requested for the above-identified application, and the priority provided in 35 USC 119 is hereby claimed:

European Patent Application No. 00202565.8, filed July 17, 2000

In support of this claim, the requisite certified copy of said original foreign application is filed herewith along with a verified English translation thereof.

It is requested that the file of this application be marked to indicate that the Applicant has complied with the requirements of 35 USC 119 and that the Patent and Trademark Office kindly acknowledge receipt of this document.

In the event any fees are required with this paper, please charge our Deposit Account No. 02-2334.

Respectfully submitted,

William M. Blackstone
Attorney for Applicants
Registration No. 29,772

Attorney Docket No. 2000.566 US
Akzo Nobel Patent Department
1300 Piccard Drive, Suite 206
Rockville, Maryland 20850-4373
Tel: (301) 948-7400
Fax: (301) 948-9751
WMB:lcf
Enclosures

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William M. Blackstone
Registration No. 29,772

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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

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Akzo Nobel N.V.
6824 BM Arnhem
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Helicobacter felis vaccine

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Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

00202565.8

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

I.L.C. HATTEN-HECKMAN

DEN HAAG, DEN
THE HAGUE, 10/07/01
LA HAYE, LE

Helicobacter felis vaccine.

The present invention relates to novel *Helicobacter* urease subunit polypeptides, nucleic acid sequences encoding these polypeptides, to the polypeptides for use in vaccines and for use in the manufacturing thereof, to vaccines comprising said polypeptides and to methods for the preparation of such vaccines. Further, the invention relates to diagnostic methods for the detection of the nucleic acid sequences, the polypeptides and antibodies against the polypeptides.

Several *Helicobacter* species are the cause of pathogenesis of the gastric epithelium. *Helicobacter pylori*, and to a lesser extent *H. heilmannii* are known to cause gastritis, a major factor in the development of peptic ulcers and gastric lymphoma in humans. *Helicobacter felis* is most likely the cause of gastric infections in both cats and dogs. In order to survive the highly acidic environment of the stomach, members of the *Helicobacter* family produce an urease that is capable of hydrolysing the urea present in gastric juice. This hydrolysation sets free an amount of NH_4OH that suffices to neutralise the environment of the bacterium. It is known, that the urease plays a role in the colonisation of the bacterium as well as in its pathogenesis.
Genes encoding urease have been described and sequenced for both *Helicobacter pylori* (Labigne et al., J. Bacteriol. 173: 1920-1931 (1991)) and *Helicobacter felis* (Ferrero et al., Molec. Microbiol. 9, 323-333 (1993)). Of the seven genes involved in urease expression and secretion, only two genes encode the two structural subunits urease A en B of the urease enzyme; ureA and ureB. These two polypeptides form a polypeptide complex having urease activity.
Vaccines against infections caused by both *H. pylori* and *felis* have been made and have been the subject of i.a. International Patent Applications WO 94/09823 and WO 96/34624. Several attempt have been made, to use *H. pylori* urease as a vaccine component for the protection of cats against *H. felis* infection. Although indeed a certain level of protection can be obtained, the results are far from the 100 % protection that would be desirable. From animal experiments published so far it becomes clear that a significant number of animals vaccinated with *H. pylori* is not at all protected against subsequent challenge with *H. felis*. Protection of cats vaccinated with purified urease from either *H. felis* or *pylori* has not been described. Vaccinating cats with *H. felis* whole cell lysates might theoretically be feasible but is not a practical option. This is because in spite of many attempts for improvement, *H. felis* is difficult to grow.
There clearly is a need for an efficacious vaccine, based upon homologous components, and it is clear that the known *H. felis* urease does not confer full protection.

It is i.a. an object of the present invention to provide a *H. felis* urease which is able to induce protection against *Helicobacter felis* infection in dogs and cats. It was surprisingly found now, that in *H. felis* a second urease exists, of which the genes encoding the structural subunits share only low homology with the known *H. felis* ureA and B genes. The novel urease is named ureaseXY, in order to discriminate it from the known urease AB. The newly found urease has been discovered in *H. felis*, and is not present in *H. pylori*.
The overall genetic structure of the genes encoding the two structural urease subunits, UreX and UreY is comparable to that of the known UreA and B in *H. felis* and *H. pylori*. The sequence homology is however surprisingly low. It was even more surprisingly found, that the homology between the ureA and B genes and the novel ureX and Y genes in one single *H. felis* strain is even strikingly lower than the homology between the various ureA and B genes from the various *Helicobacter* species.

Table 1a, 1b and 1c show the comparison of the ureX and Y gene and the polypeptides they encode form five different *Helicobacter felis* species, with the ureA and B genes and polypeptides from *Helicobacter felis*, *pylori* and *heilmannii*.

The level of homology of the genes encoding the novel structural urease subunits X and Y and the polypeptides they encode as compared to that of known ureA and B genes and polypeptide subunits is presented in table 1a, b and c.

Reference molecule : *H. felis* ureX CS1	a.a.	n.a.
H. felis ureA	50 %	57 %
H. pylori ureA	52 %	60 %
H. heilmannii ureA	54 %	62 %
H. felis strain Kukka ureX	100 %	91 %
H. felis strain Ds4 ureX	99 %	91 %
H. felis strain 2301 ureX	99 %	91 %
H. felis strain 390 ureX	99 %	91 %

Table 1a: amino acid and nucleic acid homology between the *H. felis* ureX and various ureA subunits.

Reference molecule : *H. felis* ureY CS1	a.a.	n.a.
H. felis ureB	73 %	71 %
H. pylori ureB	73 %	70 %
H. heilmannii ureB	74 %	71 %
H. felis strain Kukka ureY	99 %	95 %
H. felis strain Ds4 ureY	98 %	94 %
H. felis strain 2301 ureY	99 %	95 %

Table 1b: amino acid and nucleic acid homology between the *H. felis* ureY and various ureB subunits.

Reference molecule: *H. felis* ureXY CSI	n.a.
H. felis ureAB	67 %
H. pylori ureAB	67 %
H. heilmannii ureAB	68 %
H. felis strain Kukka ureXY	94 %
H. felis strain Ds4 ureXY	94 %
H. felis strain 2301 ureXY	94 %

Table 1c: nucleic acid homology between *H. felis* ureXY and various ureAB genes.

One embodiment of the invention thus relates to nucleic acid sequences encoding the novel urease X and Y subunits.

First of all, this embodiment of the invention relates to nucleic acid sequences encoding two subunits of a urease complex such as expressed by *Helicobacter felis*, that have at least 85 % homology with SEQ ID NO: 1, or parts thereof with a length of at least 40, preferably 45, more preferably 50 nucleotides encoding at least an immunogenic fragment of one of the subunits. Still even longer fragments, with a length of at least 55, 60 or 70 nucleic acids are in that order even more preferred.

A preferred form of this embodiment relates to nucleic acid sequences that encode the urease X subunit polypeptide or the urease Y subunit polypeptide and that have at least 85 % homology with SEQ ID NO: 1, or parts thereof with a length of at least 40, preferably 45, more preferably 50 nucleotides encoding at least an immunogenic fragment of the urease X subunit polypeptide or the urease Y subunit polypeptide. Merely as an example: the nucleic acid sequence encoding the urease X subunit of *Helicobacter felis* strain CS1 starts at position 206/207/208 (GTG) (See figure 1a (1)) and stops at position 884/885/886 (TAA). the nucleic acid sequence encoding the urease Y subunit of *Helicobacter felis* strain CS1 starts at position 897/898/899 (ATG) and stops at position 2601/2602/2603 (TAG).
Still even longer fragments, with a length of at least 55, 60 or 70 nucleic acids are in that order even more preferred.

A more preferred form of this embodiment relates to nucleic acid sequences having at least 90 %, preferably 94 %, more preferably 97 % homology therewith.

The determination of the homology percentages was done with the computer program Align Plus for Windows, available from Scientific and Educational Software, P.O.Box 72045 Durham, NC 27722-2045, USA. Settings used for the nucleic acid comparisons are indicated in figures 1a, 1b and 1c.

Since the present invention discloses nucleic acid sequences encoding novel structural *Helicobacter felis* urease subunits, it is now for the first time possible to obtain such polypeptides in sufficient quantities. This can e.g. be done by using expression systems to express the genes encoding the UreX and UreY subunits.
Therefore, in a more preferred embodiment, the invention relates to DNA fragments comprising a nucleic acid sequence according to the invention. Such DNA fragments can e.g. be plasmids, into which a nucleic acid sequence according to the invention is cloned. Such DNA fragments are useful e.g. for enhancing the amount of DNA for use as a probe, as described below.

An essential requirement for the expression of the nucleic acid sequence is an adequate promoter operably linked to the nucleic acid sequence. It is obvious to those skilled in the art that the choice of a promoter extends to any eukaryotic, prokaryotic or viral promoter capable of directing gene transcription in cells used as host cells for protein expression.
Therefore, an even more preferred form of this embodiment relates to a recombinant DNA molecule comprising a DNA fragment or a nucleic acid sequence according to the invention that is placed under the control of a functionally linked promotor. This can b obtained by means of e.g. standard molecular biology techniques. (Maniatis/Sambrook (Sambrook, J. Molecular cloning: a laboratory manual, 1989. ISBN 0-87969-309-6).

Functionally linked promotors are promotors that are capable of controlling the transcription of the nucleic acid sequences to which they are linked.
When the host cells are bacteria, useful expression control sequences which may be used include the Trp promoter and operator (Goeddel, et al., Nucl. Acids Res., 8, 4057, 1980); the lac promoter and operator (Chang, et al., Nature, 275, 615, 1978); the outer membrane protein promoter (Nakamura, K. and Inouge, M., EMBO J., 1, 771-775, 1982); the bacteriophage lambda promoters and operators (Remaut, E. et al., Nucl. Acids Res., 11, 4677-4688, 1983); the α-amylase (B. subtilis) promoter and operator, termination sequences and other expression enhancement and control sequences compatible with the selected host cell.
When the host cell is yeast, useful expression control sequences include, e.g., α-mating factor. For insect cells the polyhedrin or p10 promoters of baculoviruses can be used (Smith, G.E. et al., Mol. Cell. Biol. 3, 2156-65, 1983). When the host cell is of mammalian origin illustrative useful expression control sequences include the SV-40 promoter (Berman, P.W. et al., Science, 222, 524-527, 1983) or the metallothionein promoter (Brinster, R.L., Nature, 296, 39-42, 1982) or a heat shock promoter (Voellmy et al., Proc. Natl. Acad. Sci. USA, 82, 4949-53, 1985).

Bacterial, yeast, fungal, insect and mammalian cell expression systems are very frequently used systems. Such systems are well-known in the art and generally available, e.g. commercially through Clontech Laboratories, Inc. 4030 Fabian Way, Palo Alto, California 94303-4607, USA. Next to these expression systems, parasite-based expression systems are very attractive expression systems. Such systems are e.g. described in the French Patent Application with Publication number 2 714 074, and in US NTIS Publication No US 08/043109 (Hoffman, S. and Rogers, W.: Public. Date 1 December 1993).

Thus a still even more preferred form of this embodiment of the invention relates to Live Recombinant Carrier micro-organisms (LRCs) comprising a gene encoding the UreX or UreY polypeptide or an immunogenic fragment thereof according to the invention. Such micro-organisms are e.g. bacteria and viruses. These LRC micro-organisms are micro-organisms in which additional genetic information, in this case a gene encoding the UreX or UreY polypeptide or an immunogenic fragment thereof according to the invention has been cloned. Animals infected with such LRCs will produce an immunogenic response not only against the immunogens of the vector, but also against the immunogenic parts of the polypeptide(s) for which the genetic code is additionally cloned into the LRC, e.g. the ureX or Y gene.
As an example of bacterial LRCs, attenuated Salmonella strains known in the art can attractively be used.
Live recombinant carrier parasites have i.a. been described by Vermeulen, A. N. (Int. Journ. Parasitol. 28: 1121-1130 (1998))
Also, LRC viruses may be used as a way of transporting the nucleic acid sequence into a target cell. Live recombinant carrier viruses are also called vector viruses. The site of integration of the gene encoding a UreX or Y polypeptide may be a site in a viral gene that is not essential to the virus, or a site in an intergenic region. Viruses often used as vectors are Vaccinia viruses (Panicali et al; Proc. Natl. Acad. Sci. USA, 79: 4927 (1982), Herpesviruses (E.P.A. 0473210A2), and Retroviruses (Valerio, D. et al; in Baum, S.J., Dicke, K.A., Lotzova, E. and Pluznik, D.H. (Eds.), Experimental Haematology today - 1988. Springer Verlag, New York: pp. 92-99 (1989)).

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Cs1seq          ( 1328) ccctaccgctctagccaatggcgttacaaccatgtttggaggcggcacaggtcctgtagatggcacgaatgcgactactatcactccgggcaaatggaacttgcaccgcatgttgcgcgc
Kukkaseq        ( 1170) ..............................a........c..t........c..c.....................c.....................................
Ds4seq          ( 1124) ..............................c..t..........g.....................c.....................................
2301SEQ         ( 1123) ......................t.....................t..........g.....................c..c..................................
390seq          ( 1125) ......................t.....................t..........g.....................c..c.....................................
H. felis com    ( 1200) ......t...t.t....gc..g.............a.......a........a....cg.................c..c.........c..acgcgct..tc.aa.aa.t........t..
H. pylori co    ( 3813) ......a...t.t..a.gc..t..a.........a....t..t..a..c.......ct.........t.....................a....g.a.a..t..aa.at.g...c.ca.a..
H. heilmanni    ( 1364) ......t..ct.t..t.gc..aa.c..c......a.c..g.....g..t..a....c.........c..c..c..c..c.........c...cgc........aa.agaa...c.c.....

Cs1seq          ( 1448) agcagaagagtattctatgaatgtgggctttttgggcaaaggcaatagctctagcaaaaaacaacttgtagaacaagtagaagcgggcgcgattggtttttaaattgcatgaagactgggg
Kukkaseq        ( 1290) ..................................................t.....................................................................
Ds4seq          ( 1244) ...t..............................................c..t.....................a.................c..c.....................
2301SEQ         ( 1243) ...t..............................................c..t..........c.....................................c.....................
390seq          ( 1245) ...t.....................a.....................t.....................................................a.c..c.....................
H. felis com    ( 1320) ...c.....a..cg.c......c.a..........ct..g..g...gtg...ta.g..ccctctt.acgc..t..ga.t.....a..g.....................a.c..c.....................
H. pylori co    ( 3933) g..t.....a...........t.a..t..c....ct.....t..cgct....a.g.tgcgagct.a.cc..t...a.t.....c..t.........c......a.t..c.....................
H. heilmanni    ( 1484) tt.t.....a..cg.c.....cc.t....acc.t..t..g..g...gtg...tttg..cctgct..ca.t..c..gc.......c...........c......a.c..c.....................

Cs1seq          ( 1568) cacaacaccaagtgcgatcgatcactgcttgagcgtggcagatgaatacgatgtgcaagtttgtatccacaccgatacagtcaatgaggcaggttatgtagatgacaccctaaatgcaat
Kukkaseq        ( 1410) ......t.....................................a.....................a...........g.....................................
Ds4seq          ( 1364) ......t.........a...........................a.....................................g.....................g.....g..
2301SEQ         ( 1363) ..............................a.....................................g.....................................g..
390seq          ( 1365) ..............................a.....................................g.....................g...............g.....g..
H. felis com    ( 1440) a.gc.....tgca..t..tc.c......c.c.at..c..c.....................ggc.............cc.t..c.....g..c.g.....a.........g.g..g..
H. pylori co    ( 4053) ...c..t..ttc...a...a....tgcg..agat..t..g..ca.............cgc.........a..c..tt.g.....a..c....g......a.....ta.ggc...t..
H. heilmanni    ( 1604) ..gc.....ctca..c...a.c...gctc.a.a.a.c..t..ca.............ggcg..........c..ct.g.....a..c..c.g...g..a.........g.a..c..

Cs1seq          ( 1688) gaacgggcgcgccatccatgcctaccacattgagggagcgggtggaggacactcacctgatgttatcaccatggcaggcgagctcaatattctaccctcctccaccacccccactattcc
Kukkaseq        ( 1530) ..................................................................................ag.g.....................a.....t.....c..
Ds4seq          ( 1484) ..........................................c.....................................................a...........c..
2301SEQ         ( 1483) ..........................................c.....................................................................
390seq          ( 1485) ..........................................c.....................................................................
H. felis com    ( 1560) tgc.......a........a...t.....c...a..g..t..g..t......g.t..a.........aa........g..at.t..c.........g....t..t.a...g..c.....
H. pylori co    ( 4173) tgct..a...a.t..g..ca.t.t.....c...a..c..t..c..c......g.t.....a....t.aag.a..c..t..a.a...c.....t...g.t.....t.a.....c..c..
H. heilmanni    ( 1724) cgct..a...a.......ca...t.....cc..a..t..t..c..c......g.t.....c..g....aa.....g.....at.t..c..c..t..tg.t..t....a......c..c..

Cs1seq          ( 1808) ctataccattaatacggttgcagaacacttagacatgctcatgacatgccaccacctagacaaacgcatccgcgaggatttacaattttctcaaagccgtatccgccccggctctatcgc
Kukkaseq        ( 1650) ..........................................t.....c.............t.....................c.c...........................
Ds4seq          ( 1604) ..........................................c.............t.....................c.....................................
2301SEQ         ( 1603) ..........................................c.....................c.c..g....c.....................a.....t..
390seq          ( 1605) ..........................................c.............t..g.....................................a.....t..
H. felis com    ( 1680) t.tc....aa..c..t.aa..c..g...a.g.....t.a...gtg.........t.g..t...a.t...aag..a...g.g..g...g.cg.ttcga.g..t......caaa.......
H. pylori co    ( 4293) t.tc...g.g.....a.aa.....g...a.g.......t...gtg.........t.g..t...a....taaa..a...g.t..g..cg..g.ttcaa.g........tcaaa.c..t..
H. heilmanni    ( 1844) t.tc....aa..c..a.aa..c......a.g.......t...---.........t.g..t...aa....aaa..a...g.gg.....g.cg.ctca............caaa.c..t..

Cs1seq          ( 1928) ggctgaagatgtgctccatgatatgggtgtgatcgcgatgacaagctcggattcgcaagcaatggggcgtgcaggcgaagtgattcctcgaacttggcagactgcggataagaataaaaa
Kukkaseq        ( 1770) c.....................c.................t..c.................c..t..g...........a.........a.....a..c..........
Ds4seq          ( 1724) c.....................t..c.....................................c..t.....................................
2301SEQ         ( 1723) c.....................t..c.....................c..t..g...........a.........a.....a..c..........
390seq          ( 1725) c.....g...............t..c.....................t.....c.....................c..t..g...........a.........a.....a..........
H. felis com    ( 1800) .........ccaa.......c.....ga.ct.tt.t..c..c.....c..c..t..g..t.....a..c.t......g.....ca.a..c..........a..a..c..a..c.....
H. pylori co    ( 4413) .........cactt.g.....c.....ga.tt..t.a..c..c..t..t..c..t.....g.....c....tg..t.....t..ca..a.........a..a..t..c..a..c..g..
H. heilmanni    ( 1961) ...g......aaa.....c..c.....ga.tt..t.c..c..t.....c..c..t.....c.....t..c.tg..........ca.c..c........a..a.....c..a..c.....
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Figure 1a (3)

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Cs1seq       (  2048) agaatttggtaagcttcctgaagatggcaaagataacgataatttccgcattaagcgctacatctccaaatacactatcaaccccgctttgacccacggcgtgagcgagtatatcggctc
Kukkaseq     (  1890) ..........................tgc......t..c..c........c..a.....t.............c..t..t.............t.....................
Ds4seq       (  1844) ........................a.tgc.........c..c.....t..c..a.....................t.........c.a.....t..g..a.................
2301SEQ      (  1843) ..........................tgc......t..c..c........c..a.....t.............c..t..t.............t.....................
390seq       (  1845) ..........................tgc.........c..c........c..a.....t.............c..t..t.............t.....................
H. felis com (  1920) ...g.....gcgct.gaaa..g..aaaaggc........c..c........c..a...........t........c...........gga.cg.g..t..ga.ttct..c...g.g.....
H. pylori co (  4533) .........ccgct.gaaa.....aaaaggc........c..c...a.g..c..a......t.g..t........c..t.....a..ga.cg.t..t..ga.t.........g.a..t..
H. heilmanni (  2081) .........ccgct.g.......aaaaggc..c.....c..c........c..a.....t..t...........c........t..ca.c..a......a.ttct..a...g.......

Cs1seq       (  2168) tgtggaagagggcaagatcgccgacttggtggtgtggaatcctgccttttttggcgtaaaacccaaaatcgtgatcaaaggcggtatggtggtcttctctgaaatgggcgattctaacgc
Kukkaseq     (  2010) ..................................................................................................g.....................t..
Ds4seq       (  1964) ..............a.....t..t.....................................t..g.....t..g..t.....................................c..c.....
2301SEQ      (  1963) ..........................................t..c.....t.....................................g.....................................
390seq       (  1965) ..................................................g.....t..g..t.....t.....t..c.....................................
H. felis com (  2040) ........t......ata.......c.c...c.t....g...g..t..c......a.t..g.....t..ga.t..t..g.....at.ta.t.cgc.....c...........g.c..t..
H. pylori co (  4653) a..a....t......ag.g..t........at.....g...a..a..c.......g........c..ga.c...........at.ca.t.cg..aagcc...........g.g.....
H. heilmanni (  2201) ...a....t...t..ata...t.........c.t....gc.....g..c......a.t........c..ga.c...........t.ca.t.cgc.t...c...........g.c.....

Cs1seq       (  2288) gtctgtgcccactccccaaccggtttattaccgcgaaatgtttgggcatcacggcaaggcgaaatttgacaccagcatcacttttgtttccaaagtcgcctatgaaaatggcgtgaaaga
Kukkaseq     (  2130) ..............t..g.....................................................................................t.........
Ds4seq       (  2084) ...c.....t..a..t..g.....................................................................................................
2301SEQ      (  2083) ...........a..t..g.....................................................................----------------------------------
390seq       (  2085) ...c........g..t..g.....................................c.....................................................c...c...cg..t..ca.ggca..ga.c.....
H. felis com (  2160) ....a.t.....c..t..g..c..c.........t..........a..c..t..g..aaac.....c.......at.........c..g...c...cg..t..ca.ggca..ga.c.....
H. pylori co (  4773) t...a.c..t..c..a..............a.a........c.ct.....t..t..a..t....ac..tg.a.a............g..tc...cg..t.....c..a...a.t.....
H. heilmanni (  2321) t...a.c..............c..g..c..............c..c..c........a..c.............a.........c..g..tc....g..t........c...a.t...c.

Cs1seq       (  2408) aaagctgggcttagagcgccaagttctaccggtcaaaaactgccgtaacatcaccaagaaagacttcaagttcaacgacaaaacggcaaaaatcaccgtcgatccgaaaaccttcgaggt
Kukkaseq     (  2250) ...a..a..t.........a.g..g..c..c..g.....................g.....................t.....................................
Ds4seq       (  2204) ...a..a............a.g..g.....c..g..........c........t.............a.....a....g.....gc.t.....t........t.............
2301SEQ      (  2203) ...a..a............a.g..g.....c..g..........c........t.............a.....a....g.....gc.t.....t........t.............
390seq       (  2170) ---------------------------------------------------------------------------------------------------------------------
H. felis com (  2280) .g.a..a..gc....t...gcg.ca.cg..a..g.........t..c..t.....t..a..g...c....a........tgtg..c...c.t..tgat...a.c..tg......ata....
H. pylori co (  4893) .g.at.a..ac.t..aa.a.....gt.g.....a.....t...a.a..t.....t..a......a.gc.a..........ct..t..tc.c..tgaa...a....tg....t.a.c.t..
H. heilmanni (  2441) cg..t.......gc.aa.agtt..gt.g..t..g..........c..........a......c.t..........tgtc..c...c.c...gaa...a.c..tg......a.a.a..

Cs1seq       (  2528) ctttgtagatggcaaactctgcacctctaaacccacctcgcaagtgcctctagcccagcgctacactttcttctag
Kukkaseq     (  2370) ..........................................tg.................a...................
Ds4seq       (  2324) .....................................g....tg.....................................
2301SEQ      (  2323) .....................................g....tg.................a...................
390seq       (  2170) ----------------------------------------c...t...a...----------------------------
H. felis com (  2400) gaaa..g.........gaggta.........g.ag.agatg..t..agc.....g..a.tt..t.a...g......
H. pylori co (  5013) g..c..g.........gaagta..t........ag..aata.....agct.g..g..a.t..tt.gca.t......
H. heilmanni (  2561) gaaa..g........cgaagtt.....cc.tg.gg.tgaca..t..agc.....a..a.t...t.acc.a......
```

Figure 1a (4)

The technique of *in vivo* homologous recombination, well-known in the art, can be used to introduce a recombinant nucleic acid sequence into the genome of a bacterium, parasite or virus of choice, capable of inducing expression of the inserted nucleic acid sequence according to the invention in the host animal.

Finally another form of this embodiment of the invention relates to a host cell comprising a nucleic acid sequence encoding a polypeptide according to the invention, a DNA fragment comprising such a nucleic acid sequence or a recombinant DNA molecule comprising such a nucleic acid sequence under the control of a functionally linked promotor. This form also relates to a host cell containing a live recombinant carrier containing a nucleic acid molecule encoding a UreX or Y polypeptide or an immunogenic fragment thereof according to the invention.
A host cell may be a cell of bacterial origin, e.g. Escherichia coli, Bacillus subtilus and Lactobacillus species, in combination with bacteria-based plasmids as pBR322, or bacterial expression vectors as pGEX, or with bacteriophages. The host cell may also be of eukaryotic origin, e.g. yeast-cells in combination with yeast-specific vector molecules, or higher eukaryotic cells like insect cells (Luckow et al; Bio-technology 6: 47-55 (1988)) in combination with vectors or recombinant baculoviruses, plant cells in combination with e.g. Ti-plasmid based vectors or plant viral vectors (Barton, K.A. et al; Cell 32: 1033 (1983), mammalian cells like Hela cells, Chinese Hamster Ovary cells (CHO) or Crandell Feline Kidney-cells, also with appropriate vectors or recombinant viruses.

Another embodiment of the invention relates to the polypeptides encoded by the nucleic acid sequences, i.e. the urease X subunit and the urease Y subunit and to immunogenic fragments thereof according to the invention.

Therefore, this embodiment of the invention relates to the *Helicobacter felis* urease X polypeptide, said polypeptide having an amino acid sequence that is at least 85 % homologous to SEQ ID NO: 2 or an immunogenic fragment of that polypeptide with a length of at least 40 amino acids that is capable of inducing an immune response against ureaseXY. Preferably, the length is more than 40 amino acids, preferably at least 45, 50, 55, 60 or 70 amino acids in that order or preference.

More preferably this embodiment relates to such polypeptides having a sequence homology of at least 90 %, more preferably 95 % homology to SEQ ID NO: 2, or an immunogenic fragment of that polypeptide with a length of at least 40 amino acids that is capable of inducing an immune response against ureaseXY.

This embodiment of the invention also relates to the *Helicobacter felis* urease Y polypeptide, said polypeptide having an amino acid sequence that is at least 85 % homologous to SEQ ID NO: 3 or an immunogenic fragment of that polypeptide with a length of at least 40 amino acids that is capable of inducing an immune response against ureaseXY. Preferably, the length is more than 40 amino acids, preferably at least 45, 50, 55, 60 or 70 amino acids in that order or preference.

More preferably this embodiment relates to such polypeptides having a sequence homology of at least 90 %, more preferably 95 % homology to SEQ ID NO: 3, or an immunog nic fragment of that polypeptid with a length of at least 40 amino acids that is capable of inducing an immune response against ureaseXY.

As for the nucleotide sequence comparison, the comparison between the various amino acid sequences was made using Align Plus for Windows, available from Scientific and Educational Software, P.O.Box 72045 Durham, NC 27722-2045, USA. Settings used for the amino acid comparisons are indicated in figures 1a, 1b and 1c.

It will be understood that, for the particular polypeptides embraced herein, natural variations can exist between individual *Helicobacter felis* strains. These variations may be demonstrated by (an) amino acid difference(s) in the overall sequence or by deletions, substitutions, insertions, inversions or additions of (an) amino acid(s) in said sequence. Amino acid substitutions which do not essentially alter biological and immunological activities, have been described, e.g. by Neurath et al in "The Proteins" Academic Press New York (1979). Amino acid replacements between related amino acids or replacements which have occurred frequently in evolution are, inter alia, Ser/Ala, Ser/Gly, Asp/Gly, Asp/Asn, Ile/Val (see Dayhof, M.D., Atlas of protein sequence and structure, Nat. Biomed. Res. Found., Washington D.C., 1978, vol. 5, suppl. 3). Other amino acid substitutions include Asp/Glu, Thr/Ser, Ala/Gly, Ala/Thr, Ser/Asn, Ala/Val, Thr/Phe, Ala/Pro, Lys/Arg, Leu/Ile, Leu/Val and Ala/Glu. Based on this information, Lipman and Pearson developed a method for rapid and sensitive protein comparison (Science,227, 1435-1441, 1985) and determining the functional similarity between homologous proteins. Such amino acid substitutions of the exemplary embodiments of this invention, as well as variations having deletions and/or insertions are within the scope of the invention as long as the resulting polypeptides retain their immunoreactivity. Thus, variations not essentially influencing the immunogenicity of the polypeptide compared to the wild type polypeptide as depicted in SEQ ID NO: 2 or 3 are considered to fall within the scope of the invention. Those variations in the amino acid sequence of a certain structural subunit X or Y according to the invention that still provide a polypeptide capable of inducing an immune response against infection with *H. felis* or at least against the clinical manifestations of the infection are considered as "not essentially influencing the immunogenicity".

When a polypeptide is used for e.g. vaccination purposes or for raising antibodies, it is however not necessary to use the whole polypeptide. It is also possible to use a fragment of that polypeptide that is capable, as such or coupled to a carrier such as e.g. KLH, of inducing an immune response against that polypeptide, a so-called immunogenic fragment. An "immunogenic fragment" is understood to be a fragment of the full-length polypeptide of the structural subunit X or Y, that still has retained its capability to induce an immune response in the host, i.e. comprises a B- or T-cell epitope. At this moment, a variety of techniques is available to easily identify DNA fragments encoding antigenic fragments (determinants). The method described by Geysen et al (Patent Application WO 84/03564, Patent Application WO 86/06487, US Patent NR. 4,833,092, Proc. Natl Acad. Sci. 81: 3998-4002 (1984), J. Imm. Meth. 102, 259-274 (1987), the so-called PEPSCAN method is an easy to perform, quick and well-established method for the detection of epitopes; the immunologically important regions of the polypeptide. The method is used world-wide and as such well-known to man skilled in the art. This (empirical) method is especially suitable for the detection of B-cell epitopes. Also, given the sequence of the gene encoding any protein, computer algorithms are able to designate specific polypeptide fragments as the immunologically important epitopes on the basis of their sequential and/or structural agreement with epitopes that are now known. The determination of these regions is based on a combination of the hydrophilicity criteria according to Hopp and Woods (Proc. Natl. Acad. Sci. 78: 38248-3828 (1981)), and the secondary structure aspects according to

ALIGNED SEQUENCES

Reference molecule:		ureYCS1	1 - 568	(568 aa)	Homology	
Sequence	2:	ureYkuka	1 - 568	(568 aa)	99%	
Sequence	3:	ureYDS4	1 - 568	(568 aa)	98%	
Sequence	4:	ureY2301	1 - 568	(568 aa)	99%	
Sequence	5:	ureY390	1 - 496	(496 aa)	86%	
Sequence	6:	B felis	1 - 569	(569 aa)	73%	
Sequence	7:	B pylori	1 - 569	(569 aa)	73%	
Sequence	8:	B heilman	1 - 568	(568 aa)	74%	

Alignment type: Global Protein
Parameters: Mismatch 2; Open Gap 4; Extend Gap 1; Conserv N

```
ureYCS1      (    1) mkmkkq-eyvntygptkgdkvrlgdtdlwaevehdyttygeelkfgagktıregmgqsnspdentldlvitnamiidytgiykadıgikngkihgıgkagnkdmqdgvsphmvvgvgtea
ureYkuka     (    1) ......-.........t.....................................................................................................
ureYDS4      (    1) ......-.........t.....................................................................................................
ureY2301     (    1) ......-.........t.....................................................................................................
ureY390      (    1) ......-.........t.....................................................................................................
B felis      (    1) ..kisrk...sm....t..r.........il.....c......i...g.....d..s.t...ssye....l...l.v.............d...a..............dnnlc..pa...
B pylori     (    1) ..kisrk...sm....t..........i.........i.........g...l....s...n.skee...i....l.v.............d...a....g.........knnls..pa...
B heilman    (    1) ..kisrk...sm....t..........il.....c......i...g.....d....t...sshe.........l.v.....................l....cnrlc..pa...

ureYCS1      (  120) lagegmiitaggidshthflspqqfptalangvttmfgggtgpvdgtnattitpgkwnlhrmlraaeeysmnvgflgkgnssskkqlveqveagaıgfklhedwgttpsaidhclsvade
ureYkuka     (  120) ..........................................................................................................
ureYDS4      (  120) ..........................................................................................i.......
ureY2301     (  120) ..........................................................................................i.......
ureY390      (  120) ..........................................................................................i.......
B felis      (  121) ..a..l.v......t.i..i....i...f.s.....i......a...........ra..ks........a..l...a...v.yeps.rd.i.........i.....s..a..h...n....
B pylori     (  121) .....l.v......t.i..i....i...f.s.....i......a...........rr..kw..........l...a...a.ndas.ad.i.........i...........n.a.d...k
B heilman    (  121) ..a..l.v......t.i..i....i...f.s.i...i......a...........r...ke....s...a..l.y.....v.fepa.id.l.........i.....s.....n.a.ni..k

ureYCS1      (  240) ydvqvcihtdtvneagyvddtlnamngraihayhiegaggghspdvitmagelnilpssttptipytintvaehldmlmtchhldkriredlqfsqsrirpgsıaaedvlhdmgviamts
ureYkuka     (  240) ..........................................v.......................................................i.......
ureYDS4      (  240) ..........................................................................................i.......
ureY2301     (  240) ..........................................................................................i.......
ureY390      (  240) ..........................................................................................i.......
B felis      (  241) .....a.....l....c.e...e.ia..t..tf.t.......a....k....f....a..n....f.k..e...m....v.....s.k..v..ad.....qt.....q.....ifsi..
B pylori     (  241) .....a.....l....c.e..ma.ia..tm.tf.t.......a..i.kv...h....a..n....f.v..e...m....v.....s.k..v..ad.....qt.....t.....ifsi..
B heilman    (  241) .....a.....l....c.e...e.ia..t..tf.t.......a....k....f....a..n....f.k..e...m....-.....n.k..ve.ad.....qt.....k.....ifsi..

ureYCS1      (  360) sdsqamgrageviprtwqtadknkkefgklpedgkdndnfrikryiskytinpalthgvseyigsveegkiadlvvwnpaffgvkpkivikggmvvfsemgdsnasvptpqpvyyremfg
ureYkuka     (  360) ..............................a...........................................................................
ureYDS4      (  360) ..............................sa..........................................................................
ureY2301     (  360) ..............................a...........................................................................
ureY390      (  360) ..............................a...........................................................................
B felis      (  361) ........v....t..............r.k.ekg.................gia..i.d.v....v..y....l.s.....i..nmi....fial.q...a...i.............
B pylori     (  361) ........v....t..............r.k.ekg..........l........ia..i...v....v..v....l.s........nmi....fial.q...a...i............a
B heilman    (  360) ........v....t..............r...ekg..................i...i...v....v..y....l.s.....i..nmi....fial.q...a...i.............
```

Figure 1c (1)

11/15/99 ALIGNED SEQUENCES

Reference molecule:	ureXCS1	1 -	226	(226 aa)	Homology	
Sequence 2:	ureXkuka	1 -	226	(226 aa)	100%	
Sequence 3:	ureXDS4	1 -	226	(226 aa)	99%	
Sequence 4:	ureX2301	1 -	226	(226 aa)	99%	
Sequence 5:	ureX390	1 -	226	(226 aa)	99%	
Sequence 6:	A felis	1 -	237	(237 aa)	50%	
Sequence 7:	A pylori	1 -	238	(238 aa)	52%	
Sequence 8:	A heilman	1 -	234	(234 aa)	54%	

Alignment type: Global Protein
Parameters: Mismatch 2; Open Gap 4; Extend Gap 1; Conserv N

```
ureXCS1     (   1) vkltpkeqekfllyyagevarkrkaeglklnqpeaiayisahimdearrgkktvaqlmeecmhflkkdevmpgvgnmvpdlgveatfpdgtklvtvnwpiepdehfkagevkfgcdkdie
ureXkuka    (   1) .... ..................................................e.....................................................................
ureXDS4     (   1) .....................................................e.....................................................................
ureX2301    (   1) ?.....................................................e.....................................................................
ureX390     (   1) .....................................................e.....................................................................
A felis     (   1) m.....ld.lm.h...rl.eeal.r.v...yt..v.l..grv.ek..d.n.s..d..q.grtw...en..d..as.ihev.i..n.........iht.v.dngklap...-.lkne..t
A pylori    (   1) m.....ld.lm.h....l.k...ek.i...yv..v.l.....e...a....a.e..q.grtl..p.d..d..as.ihev.i..m.........ht...angklvp..-l.lkne..t
A heilman   (   1) m.....ld.lm.h....l.kq...k.i...yt..v.l....v.e...a...s..d..q.grtl..a.d.....ah.ihev.i..g.........iht.v.agsdkl.pgevilkne..t

ureXCS1     (  121) lnagkevtelevtnegpkslhvgshfhffeankalkfdrekaygkrldipsgntlrigagqtrkvqlıplggskkvigmnglvnniaderhkhkaldkakshgfi----------k
ureXkuka    (  121) ..........................................................................................----------.
ureXDS4     (  121) ..........................................................................e.........----------.
ureX2301    (  121) ..........................t.....................................................................----------.
ureX390     (  121) ..v.......................t.....................................................................----------.
A felis     (  120) i.....ais.k.k.k.drpvq.........v..l.d...a.sfc.....a..tav.fep.eeks.e..di..n.riy.f.s..drq..adg.klg.kr..ek..gsvncgceatkdk-q
A pylori    (  120) i.e..kavsvk.k.v.drpvqi........v.rc.d.....tf......a..tav.fep.eeks.e..di..nrrif.f.a..drq..nes.ki..hr..er..hgaksddnyvktike
A heilman   (  121) .....havq.k.k.k.drpvq.........v..l.d.............a..tav.fep.eekt.e..di..n.riy.f.a..drq..hdg.kl..kr..ekh.gtincgcdn-----.
```

Figure 1b

Chou and Fasman (Advances in Enzymology 47: 45-148 (1987) and US Patent 4,554,101). T-cell epitopes can likewise be predicted from the sequence by computer with the aid of Berzofsky's amphiphilicity criterion (Science 235, 1059-1062 (1987) and US Patent application NTIS US 07/005,885). A condensed overview is found in: Shan Lu on common principles: Tibtech 9: 238-242 (1991), Good et al on Malaria epitopes; Science 235: 1059-1062 (1987), Lu for a review; Vaccine 10: 3-7 (1992), Berzowsky for HIV-epitopes; The FASEB Journal 5:2412-2418 (1991).

Vaccines against e.g. *Helicobacter pylori*, which has only one urease, can be made on the basis of this urease, as was described above. In the specific case of *Helicobacter felis* however a vaccine based upon the known *Helicobacter felis* structural subunits ureA and B is not capable of providing sufficient protection against *Helicobacter felis* infection: immunity against structural subunits ureA and B allegedly does not neutralise the urease activity of the newly found heterologous structural subunits UreX and Y.

Therefore, vaccines for the protection of animals against *Helicobacter felis* infection should at least be directed against the novel urease XY.
Therefore, one form of still another embodiment of the invention relates to vaccines capable of protecting mammals such as dogs and cats against *Helicobacter felis* infection, that comprise the structural subunit X or Y, preferably X and Y, more preferably X, Y, A and B, or an immunogenic fragment of X and/or Y according to the invention together with a pharmaceutically acceptable carrier.

Still another embodiment of the present invention relates to the polypeptides according to the invention for use in a vaccine.

In still another embodiment, the polypeptide according to the invention is for use in the manufacturing of a vaccine for combating *Helicobacter felis* infections.

One way of making a vaccine according to the invention is by biochemical purification of the ureaseXY polypeptide or its subunits from a bacterial culture. This can e.g. be done by centrifugation of the bacteria, and the use of gel-filtration columns for separation of the urease polypeptide or its subunits from other components. Further purification may e.g. be done by selective precipitation in ammonium-sulphate, followed by centrifugation, gel electrophoresis and, if desired, separation from the urease AB subunits and dissolving the pellet in a suitable buffer. This is however a time-consuming way of making the vaccine, especially where *Helicobacter felis* is difficult to grow.

It is therefore much more convenient to use the expression products of the genes encoding the urease X and Y subunits according to the invention in vaccines.
Such vaccines can easily be made by admixing ureaseXY or an UreX or Y subunit or an immunological fragment thereof according to the invention with a pharmaceutically acceptable carrier as described below.

Furthermore vaccines can comprise live recombinant carriers as described above, capable of expressing ureaseXY, an UreX or UreY subunit or immunogenic fragments thereof according to the invention. Such vaccines, e.g. based upon a Salmonella carrier or a viral carrier infecting the gastric epithelium have the advantage over subunit vaccines that they better mimic the natural way of infection of *Helicobacter felis*.
Moreover, their self-propagation is an advantage since only low amounts of the recombinant carrier are n cessary for immunisation.

Vaccines described above all contribute to active vaccination, i.e. the host's immune system is triggered by the UreX and/or Y polypeptide or immunogenic fragments thereof, to make antibodies against these polypeptides.
Alternatively, such antibodies can be raised in e.g. rabbits or can be obtained from antibody-producing cell lines as described below. Such antibodies can then be administered to the host animal. This method of vaccination, passive vaccination, is the vaccination of choice when an animal is already infected, and there is no time to allow the natural immune response to be triggered. It is also the preferred method for vaccinating immune-compromised animals. Administered antibodies against *Helicobacter* UreX or UreY can in these cases bind directly to the urease excreted by the bacteria. This has the advantage that the urease activity is directly eliminated, thus resulting in acidification of the environment and decreased or stopped *Helicobacter* growth.
Therefore, one other form of this embodiment of the invention relates to vaccines comprising antibodies against *Helicobacter felis* urease X polypeptides that have an amino acid sequence that is at least 85 % homologous to SEQ ID NO: 2 or immunogenic fragments of that polypeptide with a length of at least 40 amino acids that are capable of inducing an immune response against ureaseXY or antibodies against *Helicobacter felis* urease Y polypeptides that have an amino acid sequence that is at least 85 % homologous to SEQ ID NO: 3 or immunogenic fragments of that polypeptide with a length of at least 40 amino acids that are capable of inducing an immune response against ureaseXY.

Vaccines can also be based upon host cells as described above, that comprise ureaseXY, an UreX or UreY subunit or immunogenic fragments thereof according to the invention.

An alternative and efficient way of vaccination is direct vaccination with DNA encoding the relevant antigen. Direct vaccination with DNA encoding polypeptides has been successful for many different polypeptides. (As reviewed in e.g. Donnelly et al., The Immunologist 2: 20-26 (1993)).
This way of vaccination is very attractive for the vaccination of both cats and dogs against *Helicobacter felis* infection.
Therefore, still other forms of this embodiment of the invention relate to vaccines comprising nucleic acid sequences encoding a polypeptide according to the invention or immunogenic fragments thereof according to the invention, and to vaccines comprising DNA fragments that comprise such nucleic acid sequences.
Still other forms of this embodiment relate to vaccines comprising recombinant DNA molecules according to the invention.
DNA vaccines can easily be administered through intradermal application e.g. using a needle-less injector. This way of administration delivers the DNA directly into the cells of the animal to be vaccinated. Amount of DNA in the microgram range between 1 and 100 µg provide very good results.

In a further embodiment, the vaccine according to the present invention also comprises antigens from other dog or cat pathogenic organisms and viruses, or genetic information encoding such antig ns. Such organisms and viruses are .g. Feline Infectious Peritonitis virus, Feline Immune deficiency virus, Canine and Feline Parvovirus, Distemper virus, Ad novirus, Calicivirus, *Bordetella bronchiseptica, Borrelia burgdorferi, Leptospira interrogans, Chlamydia* and *Bartonella henseli.*

Also, the present invention relates to polypeptides according to the invention for use in the manufacturing of a vaccine for combating *Helicobacter felis* infections.

All vaccines according to the present invention comprise a pharmaceutically acceptable carrier. A pharmaceutically acceptable carrier can be e.g. sterile water or a sterile physiological salt solution. In a more complex form the carrier can e.g. be a buffer.

Vaccines according to the present invention may in a preferred presentation also contain an adjuvant. Adjuvants in general comprise substances that boost the immune response of the host in a non-specific manner. A number of different adjuvants are known in the art. Examples of adjuvants are Freunds Complete and Incomplete adjuvant, vitamin E, non-ionic block polymers, muramyldipeptides, Quill A(R), mineral oil e.g. Bayol(R) or Markol(R), vegetable oil, and Carbopol(R) (a homopolymer), or Diluvac(R) Forte.
The vaccine may also comprise a so-called "vehicle". A vehicle is a compound to which the polypeptide adheres, without being covalently bound to it. Often used vehicle compounds are e.g. aluminium hydroxide, -phosphate or -oxide, silica, Kaolin, and Bentonite.
A special form of such a vehicle, in which the antigen is partially embedded in the vehicle, is the so-called ISCOM (EP 109.942, EP 180.564, EP 242.380)
In addition, the vaccine may comprise one or more suitable surface-active compounds or emulsifiers, e.g. Span or Tween.
Often, the vaccine is mixed with stabilisers, e.g. to protect degradation-prone polypeptides from being degraded, to enhance the shelf-life of the vaccine, or to improve freeze-drying efficiency. Useful stabilisers are i.a. SPGA (Bovarnik et al; J. Bacteriology 59: 509 (1950)), carbohydrates e.g. sorbitol, mannitol, trehalose, starch, sucrose, dextran or glucose, proteins such as albumin or casein or degradation products thereof, and buffers, such as alkali metal phosphates.
In addition, the vaccine may be suspended in a physiologically acceptable diluent.
It goes without saying, that other ways of adjuvating, adding vehicle compounds or diluents, emulsifying or stabilising a polypeptide are also embodied in the present invention.

Vaccines according to the invention that comprise the UreX or UreY subunit polypeptide can very suitably be administered in amounts ranging between 1 and 100 micrograms, although smaller doses can in principle be used. A dose exceeding 100 micrograms will, although immunologically very suitable, be less attractive for commercial reasons.

Vaccines based upon live attenuated recombinant carriers, such as the LRC-viruses and bacteria described above can be administered in much lower doses, because they multiply themselves during the infection. Therefore, very suitable amounts would range between 10^3 and 10^9 CFU/PFU for respectively bacteria and viruses.

Many ways of administration can be applied. Intranasal application is a frequently used way of administrating a vaccine. Oral application is also an attractive way of administration, because the infection is often located in the upper digestive tract. A preferred way of oral administration is the packaging of the vaccine in capsules, known and frequently used in the art, that only disintegrate in the highly acidic environment of the stomach. Also, the vaccine could be mixed with compounds known in the art for temporarily enhancing the pH of the stomach.

Systemic application is also suitable, e.g. by intramuscular application of the vaccine. If this route is followed, standard procedures known in the art for systemic application are well-suited.

Another embodiment of the invention relates to diagnostic tests for the detection of *H. felis* infection. It is known that several *Helicobacter* species such as *H. bizzozeronii, H. felis* and *H. salomonis* are capable of infecting both cats and dogs. Of these three, *H. felis* is the species suspected to cause most of the pathology, although it is often outnumbered by *H. bizzozeronii* and *H. salomonis*. Thus, a quick and correct diagnosis of disease, in both cats and dogs, caused by *Helicobacter felis* is important. It has however been very difficult to discriminate between these three species due to the fact that they are so very closely related.
Therefore it is another objective of this invention to provide such diagnostic tools suitable for discriminating *H. felis* from other *Helicobacter* species.

On the basis of the novel urease polypeptides and the genes encoding the urease polypeptides, at least three different diagnostic tests, specifically suitable for the discrimination of *H. felis* from other members of the *Helicobacter* family were developed:
1) a diagnostic test based upon the presence or absence of DNA encoding the specific UreX and UreY structural subunits
2) a diagnostic test based upon the detection of antibodies against the specific UreX and UreY structural subunits
3) a diagnostic test based upon the detection of antigenic material of the specific UreX and UreY structural subunits

A diagnostic test according to 1) is e.g. based upon the reaction of bacterial DNA isolated from the animal to be tested, with specific probes or PCR-primers based upon the sequence of ureX or Y genes. If *H. felis* DNA is present in the animal, this will e.g. specifically bind to ureX or Y specific PCR-primers and will subsequently become amplified in PCR-reaction. The PCR-reaction product can then easily be detected in DNA gel electrophoresis.
The DNA can most easily be isolated from the micro-organisms present in swabs of the upper digestive tract or in the saliva of the animal to be tested. Specific primers can easily be selected from the many regions of the ureX and ureY coding sequences and the non-coding intergenic sequence that differ in sequence from the comparable regions in the ureAB coding sequences. One of the many algorithms suitable for the determination of the level of nucleic acid homology and for comparison of nucleotide sequences in general is known as "Clustal W". It has been described by Thompson et al., in Nucleic Acid Research 22: 4673-4680 (1994). The program can be found at several sites on Internet. An more recent alternative for this program is e.g. Align Plus for Windows, available from Scientific and Educational Software, P.O.Box 72045 Durham, NC 27722-2045, USA.
As follows from figure 1, a large number of possible PCR-primers can be found that are specific for ureX or ureY. An extremely specific pair of PCR-probes is e.g. formed by the 5'-located sequence CATGCACTTTTTGAAAAAAGA (SEQ ID NO: 16) and the 3'-located sequence TATGGTGGTCTTCTCT (SEQ ID NO: 17). Of course many other sequences that are specific for ureX or Y or the intergenic region are suitable. Standard PCR-textbooks give methods for determining the suitability of the probes for selective PCR-reactions with ureX or ureY. PCR-techniques are extensively described in (Dieffenbach & Dreksler; PCR primers, a laboratory manual. ISBN 0-87969-447-5 (1995)).

Another DNA-based test is based upon growth of bacterial material obtained from the swab, followed by classical DNA purification followed by classical hybridisation with radioactively or colour-labelled ureXY-specific DNA-fragments. Given the very low homology between the ureXY-coding regions and the ureAB coding regions of both *H. felis* and other *Helicobacter* species, hybridisation unambiguously indicates the presence or absence of *H. felis*. Both PCR-reactions and hybridisation reactions are well-known in the art and are i.a. described in Maniatis/Sambrook (Sambrook, J. *et al.* Molecular cloning: a laboratory manual. ISBN 0-87969-309-6).

Selective detection with PCR-primers or with classical hybridisation with ureXY-specific DNA-fragments can be done with fragments that preferably are short, but for practical reasons preferably consist of a stretch of at least 10 contiguous nucleotides of SEQ ID NO: 1. It is clear that for hybridisation experiments a probe needs to be selected that has a higher homology to SEQ ID NO: 1, than to sequences encoding the *Helicobacter* ureA or ureB subunit. Such a probe can very easily be selected with the help of the Align Plus for Windows program or the Clustal W program as discussed above. In a comparative hybridisation experiment the DNA to be diagnosed can be tested next to e.g. H. *pylori* DNA. The probe according to the invention, having a higher homology to SEQ ID NO: 1 than to a gene encoding ureAB, would bind better to *H. felis* DNA (if present in the sample) than to DNA of other *Helicobacter* species thus specifically revealing the presence of H. *felis* DNA in the sample to be tested. The sequences SEQ ID NO: 16 or 17 mentioned above are merely examples of probes very suitable for labelling and subsequent use in the *H. felis*-specific hybridisation assays as described.

Thus, one embodiment of the invention relates to a diagnostic test for the detection of DNA encoding the specific *Helicobacter* UreX and UreY subunit polypeptides. Such a test comprises a nucleic acid sequence according to the invention or a fragment thereof that is specific for the DNA encoding UreX and UreY or the intergenic region between UreX and UreY. A fragment that is specific for that DNA is a fragment that binds better to the DNA encoding UreX and UreY or the intergenic region between UreX and UreY than to the DNA encoding UreA and UreB or the intergenic region between UreA and UreB.

Methods for the detection of *Helicobacter felis* DNA comprise hybridisation of the DNA to be tested with UreX or Y DNA, or PCR-reaction of the DNA to be tested with UreX or Y DNA specific probes.

A diagnostic test according to 2) for the detection of *Helicobacter felis* antibodies in sera can be e.g. a simple sandwich-ELISA-test in which purified UreX or UreY subunit polypeptides or antigenic fragments thereof according to the invention are coated to the wall of the wells of an ELISA-plate. A method for the detection of such antibodies is e.g. Incubation of purified UreX or Y polypeptide with serum from mammals to be tested, followed by e.g. incubation with a labelled antibody against the relevant mammalian antibody. A colour reaction can then reveal the presence or absence of antibodies against *Helicobacter felis* urease XY. Depending on the labelled antibodies used, the selectivity of this system can be improved by pre-incubation of the serum to be tested with urease AB followed by spinning down the precipitate, in order to avoid non-XY-specific reactions.
If antigenic fragments of the UreX or UreY structural subunits according to the invention are used for coating, this pre-incubation step can be skipped.

Another example of a diagnostic test system is e.g. the incubation of a Western blot comprising UreX or UreY polypeptide or an antigenic fragment thereof according to the invention, with serum of mammals to be tested, followed by analysis of the blot.
The purified UreX and UreY structural subunits or antigenic fragments thereof according to the invention, suitable for the coating of ELISA plates or for Western blotting can easily be obtained by expression of the ureX and ureY gene as was described by Ferrero for ureA and B (Ferrero et al., Molec. Microbiol. 9, 323-333 (1993)).

Also, the invention relates to methods for the detection in serum of antibodies against *Helicobacter felis* antibodies in which the method comprises the incubation of serum with UreX or UreY polypeptide or an antigenic fragment thereof according to the invention.

A diagnostic test according to 3) based upon the detection of antigenic material of the specific UreX and UreY structural subunits of *Helicobacter felis* antigens and therefore suitable for the detection of *Helicobacter felis* infection can e.g. also be a standard ELISA test. In one example of such a test the walls of the wells of an ELISA plate are coated with antibodies directed against the specific UreX and UreY structural subunits of *Helicobacter felis.* The antigenic material to be tested can if necessary be pre-incubated with antibodies against UreA and B. This will leave the UreX and Y specific epitopes uncovered and therefore the pre-incubated *Helicobacter* species will bind to the ELISA plate only if it comprises UreX or Y, i.e. if it specifically is *Helicobacter felis.*
The use of monoclonal antibodies specific for UreX or Y and not reacting with UreA or B are the preferred antibodies in such tests, because they make the pre-incubation step superfluous. Such monoclonal antibodies can easily be obtained by immunising inbred mice with immunising fragments of UreX or Y according to the invention, by techniques also known in the art (See below: Kohler and Milstein).

The polypeptides or immunogenic fragments thereof according to the invention expressed as characterised above can be used to produce antibodies, which may be polyclonal, monospecific or monoclonal (or derivatives thereof). If polyclonal antibodies are desired, techniques for producing and processing polyclonal sera are well-known in the art (e.g. Mayer and Walter, eds. *Immunochemical Methods in Cell and Molecular Biology*, Academic Press, London, 1987).
Monoclonal antibodies, reactive against the polypeptide according to the invention (or variants or fragments thereof) according to the present invention, can be prepared by immunising inbred mice by techniques also known in the art (Kohler and Milstein, *Nature*, 256, 495-497, 1975).

Finally, the invention relates to methods for the detection of antigenic material from *Helicobacter felis* in which the method comprises the incubation of serum, tissue of body fluids with antibodies against UreX or UreY polypeptide or an antigenic fragment thereof according to the invention.

Example 1

The *ureX* and *ureY* genes of *Helicobacter felis* strain CS1: cloning and expression in *Escherichia coli*.

The *ureX* and *ureY* genes of *H. felis* strain CS1 were cloned as an operon into an *E. coli* T7 expression vector, pET3a, as follows:

For proper expression of the UreX and Y proteins in pET3a (Novagen, 601 Science Drive, Madison WI, USA) the genes were cloned as a *Nde*I-*Bam*HI DNA fragment into the *Nde*I-*Bam*HI sites of this vector. The *ureaseXY* operon contains an internal *Nde*I site that was mutated by overlap-extension PCR of 2 PCR fragments. For that purpose two PCR fragments (the 5' and the 3' products) were amplified using chromosomal DNA of H. *felis* CS1 as the template. The 5' PCR product contained the complete *ureX* gene and the first part of the *ureY* gene. The forward primer contained a *Nde*I restriction site and the start codon of ureX (GGAGTAACATATGAAACTCACA CCCAAAGAGC) (SEQ ID NO: 18), and the reverse primer contains a point mutation (CACACCC ACGACCATGTGAGGGCTTAC) (SEQ ID NO: 19). The second, 3' PCR product consisted of the 3' end of the *ureY* gene. This forward primer is complementary to the reverse primer of the first PCR product and also contained the same point mutation (GTAAGCC CTCACATGGTCGTGGGTGTG) (SEQ ID NO: 20), and the reverse primer contained a *Bam*HI restriction site just downstream of the stopcodon of the *ureY* gene (CGAATT CGGATCCTAGAAGAAAGTGTAGCGCTGG) (SEQ ID NO: 21). The mutation in the complementary primers is made to delete the internal *Nde*I site in *ureY*, it replaces the CATATG (His- Met) by CACATG (His-Met).

After amplification of both PCR products, the complete operon was obtained by overlap-extension-PCR with the forward primer of the *ureX* and the reverse primer of the *ureY* using both PCR products as templates. The resulting PCR product was cloned into PCR-bluntII-TOPO (Invitrogen, P.O.Box 2312, 9704 CH Groningen, The Netherlands) and transformed into *E. coli* TOP10F' cells (Invitrogen). Positive clones were isolated and the *urease*XY genes were sub-cloned into pET3a with *Nde*I-*Bam*HI. The obtained plasmid was called pUreXY-1 and was transformed into the expression strain HMS174(DE3)/pLysS (Novagen).

The *ureX* and *ureY* genes of pUreXY-1 were expressed in HMS174(DE3)/pLysS as follows: an overnight culture was diluted 1/100 into TB Amp^{100} Cam^{25}; this culture was incubated for 3 h at 37°C at 200 rpm; the culture was induced by adding 1 mM of IPTG and incubated for another 3 h at 37°C at 200 rpm. The induction was done twice, once in a small scale and once in a large scale.

The induced samples were analysed on a SDS-PAGE gel (fig. 2). As can be clearly seen from lane 9, expression of UreX and UreY, when induced provides the two structural subunits as polypeptide bands with a molecular weight of 25 kDa for the UreX subunit and 62 kDa for the UreY subunit.

Legend to the figures

Figure 1a: Comparison of the nucleic acid sequence encoding UreX and Y, including a short non-coding region bridging the two coding sequences, from *Helicobacter felis* species CS1, Kukka, Ds4, 2301 and 390 with the nucleic acid sequence encoding UreA and B, including a short non-coding region bridging the two coding sequences, from *Helicobacter felis*, *pylori* and *heilmannii*

Figure 1b: Comparison of the amino acid sequence of UreX from *Helicobacter felis* species CS1, Kukka, Ds4, 2301 and 390 with the amino acid sequence encoding UreA from *Helicobacter felis*, *pylori* and *heilmannii*

Figure 1c: Comparison of the amino acid sequence of UreY from *Helicobacter felis* species CS1, Kukka, Ds4, 2301 and 390 with the amino acid sequence encoding UreB from *Helicobacter felis*, *pylori* and *heilmannii*

Figure 2: Polyacrylamide gel of the expression products UreX and UreY

Lane 7 : Biorad broad range marker
Lane 8 : Complete cell culture before induction (small scale culture)
Lane 9 : Complete cell culture after induction (small scale culture)
Lane 10 : Complete cell culture after induction (large scale culture)
Lane 11 : Supernatant after induction (large scale culture).
Lane 12 : Biorad pre-stained marker

against ureaseXY.

12) Polypeptide according to claims 8-11 fur use in a vaccine

13) Polypeptide according to claims 8-11 for use in the manufacturing of a vaccine for combating *Helicobacter felis* infections.

14) Vaccine for combating *Helicobacter felis* infections, characterised in that it comprises a nucleic acid sequence according to claims 1-3, a DNA fragment according to claim 4, a recombinant DNA molecule according to claim 5, a live recombinant carrier according to claim 6, a host cell according to claim 7 or a polypeptide according to claims 8-11, and a pharmaceutically acceptable carrier.

15) Vaccine according to claim 14, characterised in that it comprises an adjuvant.

16) Vaccine according to claim 14 or 15, characterised in that it comprises an additional antigen derived from a virus or micro-organism pathogenic to mammals or genetic information encoding said antigen.

17) Vaccine according to claim 16, characterised in that said virus or micro-organism pathogenic to mammals is selected from the group of Feline Infectious Peritonitis virus, Feline Immune deficiency virus, Canine and Feline Parvovirus, Distemper virus, Adenovirus, Calicivirus, *Bordetella bronchiseptica, Borrelia burgdorferi, Leptospira interrogans, Chlamydia* and *Bartonella henseli.*

18) Vaccine for combating *Helicobacter felis* infections, characterised in that it comprises antibodies against a polypeptide according to claims 8-11.

19) Method for the preparation of a vaccine according to claims 14-17, said method comprising the admixing of a polypeptide according to claims 8-11 and a pharmaceutically acceptable carrier.

20) Diagnostic test for the detection of *Helicobacter felis* specific DNA characterised in that the test comprises a nucleic acid sequence according to claims 1-3, or a fragment thereof.

21) Diagnostic test for the detection of antibodies against *Helicobacter felis*, characterised in that said test comprises a polypeptide or a fragment thereof as described in claims 8-11.

22) Diagnostic test for the detection of antigenic material of *Helicobacter felis*, characterised in that said test comprises antibodies against a polypeptide or a fragment thereof as described in claims 8-11.

Claims

1) Nucleic acid sequence encoding two subunit polypeptides of a urease complex such as expressed by *Helicobacter felis*, said nucleic acid sequence having at least 85 % homology with SEQ ID NO: 1, or a part thereof encoding at least an immunogenic fragment of one of said subunits, said part having a length of at least 40, preferably 45, more preferably 50 nucleotides.

2) Nucleic acid sequence according to claim 1, characterised in that it encodes the urease X subunit polypeptide or the urease Y subunit polypeptide.

3) Nucleic acid sequence according to claim 1 or 2, characterised in that the sequence has at least 90 %, preferably 94 %, more preferably 97 % homology therewith.

4) DNA fragment comprising a nucleic acid sequence according to claims 1-3

5) Recombinant DNA molecule comprising a nucleic acid sequence according to claims 1-3 or a DNA fragment according to claim 4, under the control of a functionally linked promoter.

6) Live recombinant carrier comprising a recombinant DNA molecule according to claim 5

7) Host cell comprising a nucleic acid sequence according to claims 1-3, a DNA fragment according to claim 4, a recombinant DNA molecule according to claim 5 or a live recombinant carrier according to claim 6.

8) *Helicobacter felis* urease X subunit polypeptide, said polypeptide having an amino acid sequence that is at least 85 % homologous to SEQ ID NO: 2 or an immunogenic fragment of said polypeptide with a length of at least 40, preferably 45, more preferably 50 amino acids said immunogenic fragment being capable of inducing an immune response against ureaseXY.

9) Polypeptide according to claim 8, having a sequence homology of at least 85 %, preferably 90 %, more preferably 95 % homology to SEQ ID NO: 2, or an immunogenic fragment of said polypeptide capable of inducing an immune response against ureaseXY.

10) *Helicobacter felis* urease Y subunit polypeptide, said polypeptide having an amino acid sequence that is at least 85 % homologous to SEQ ID NO: 3 or an immunogenic fragment of said polypeptide with a length of at least 40, preferably 45, more preferably 50 amino acids said immunogenic fragment being capable of inducing an immune response against ureaseXY.

11) Polypeptide according to claim 10, having a sequence homology of at least 85 %, preferably 90 %, more preferably 95 % homology to SEQ ID NO: 3, or an immunogenic fragment of said polypeptide capable of inducing an immune response

Abstract

The present invention relates to novel *Helicobacter felis* urease subunit polypeptides and to nucleic acid sequences encoding these subunit polypeptides, to DNA fragments and recombinant DNA molecules comprising the nucleic acid sequences encoding these subunit polypeptides, to live recombinant carriers and to host cells comprising nucleic acid sequences encoding these subunit polypeptides. Also, the invention relates to the subunit polypeptides for use in vaccines and for use in the manufacturing thereof, to vaccines comprising said subunit polypeptides and to methods for the preparation of such vaccines. Furthermore, the invention relates to diagnostic methods for the detection of *Helicobacter felis* specific nucleic acid sequences, *Helicobacter felis* antigenic material and to antibodies against *Helicobacter felis*.

ALIGNED SEQUENCES

Reference molecule:		Cs1seq	206 -	2603	(2398 bps)	Homology
Sequence	2:	Kukkaseq	48 -	2445	(2398 bps)	94%
Sequence	3:	Ds4seq	2 -	2399	(2398 bps)	94%
Sequence	4:	2301SEQ	1 -	2398	(2398 bps)	94%
Sequence	5:	390seq	3 -	2181	(2179 bps)	85%
Sequence	6:	H. felis comp	43 -	2475	(2433 bps)	67%
Sequence	7:	H. pylori com	2659 -	5088	(2430 bps)	67%
Sequence	8:	H. heilmannii	211 -	2636	(2426 bps)	68%

Alignment type: Global DNA
Parameters: Mismatch 1; Open Gap 3; Extend Gap 3

```
Cs1seq          (  206) gtgaaactcacacccaaagagcaagaaaagttcttgttatattatgcgggcgaagtggctagaaagcgcaaagcagagggcttaaagctcaaccaacccgaagccattgcttacattagt
Kukkaseq        (   48) ..............................................................................................................c.........
Ds4seq          (    2) ..............................................................g...............................................c.........
2301SEQ         (    1) .w............................................................................................t..............c.........
390seq          (    3) ..............................................................................................t..............c.........
H. felis com    (   43) a.......a..g..t.....a.t...c.....aa..c.cc...........ag.t....aga.g.agcgttg..gcgt..tg.g..a.....tt.ca.......gg.c..gct......c
H. pylori co    ( 2659) a..........c..a......tt...t.....ga..c.cc.c..c..t..a...t......a...a.......a.a.a...a.t.....t...t.tgta.....ag.a....tg......
H. heilmanni    (  211) a.......g.....t......ttg..t.....ga..c.cc..............c.a..c.a.c.a.........a.a...a.t.....a...t.ca.......tg.a..act......c

Cs1seq          (  326) gcccatattatggacgaagcgcgccgtggaaaaaaaaccgttgcccagcttatggaagagtgcatgcacttttgaaaaaagatgaagtaatgcccggggtgggtaatatggttcccgat
Kukkaseq        (  168) ................g.....t.....c.............gg.a.............t.....................c..g..g..............g........c..t...
Ds4seq          (  122) ................g.............c.....g........gg.a.............t.....................c..g..g........t.....g........c..t...
2301SEQ         (  121) ................g...........c.............tg.a...........a..t.....................g..g........t.....g........c..t...
390seq          (  123) ................g...........c.............tg.a...........a..t.....................g..g........t.....g........c..t...
H. felis com    (  163) .gg.g.g.g.....aa.g.....tga...t..t....g...g..gg.tt.g...c....ag...g.act.ggc.t.........aa.t..g...ga...c..a.ca.gc...a...at..a
H. pylori co    ( 2779) ..............a......a.agc...t.....g..t.cg..tg.at.g...c....ag.gcgcactc....a...cc......t..g...gat..c....ca.gc...a.c.at..a
H. heilmanni    (  331) ......g.c.....a..g..c...gcc..t.......g...g..gg.tt.g...c....ag...g.act..ac.c...gcc.....t..g.....t..c....cgc.....a.c.a...a

Cs1seq          (  446) ctaggtgtagaagccacctttcctgatggtacgaaacttgtaactgtgaattggcccatcgaaccagatgagcacttcaaagcgggcgaagtgaaatttggttgcgataaagacatcgag
Kukkaseq        (  288) t.g..c..g.......t..c..c.....c..c.....c.........................t.....a.....t..g.....t.............c..t...........t..a
Ds4seq          (  242) t....c..g.....t..t.....c.....c..c.....c.....c.....a.....................c.....c..t...........t..a
2301SEQ         (  241) t.g..c...........t..c..c.....c..c.....c.....c.............t.....t.....a.....t.....c..t.............c..t...........t...
390seq          (  243) t.g..c...........t..c..c.....c..c.....c.....c.............t.....t.....a.....t.....c..t.............c..t...........t...
H. felis com    (  283) g.g..ga.t.....t.a...c..c.....a..c..g.........a.cc.cact..gg.a..ggata...gca.a..agccc.c.....g..---c..cttaaaaa..g.g.....tact
H. pylori co    ( 2899) g.g...a.t.....g.tg.....g..t.....c.....c...c..acc..t..t..gg.ca...gta.a..agttc.t..t..gt..---..cttaaaaa..g........act
H. heilmanni    (  451) g.g..ga.t.....ggg.....c.....g..a...t.a..g..ca.cc.cact...g.a...g.t.gcagcg..aagctt..tcc..gt.aagtga.cctcaaaa.cg.....acc

Cs1seq          (  566) ctcaatgcaggcaaagaagtaaccgaacttgaggttactaatgaagggcctaaatccttgcatgtgggtagccatttccacttctttgaagctaacaaggcactaaaattcgatcgtgaa
Kukkaseq        (  408) .....c.....t..g.....t.........a..a.....c.....a.....................................c.....a...t.g..........g...
Ds4seq          (  362) .....c.....t..g.....t.........a..a.....c..c.....a.....................................c.........t.g..........g...
2301SEQ         (  361) .....c..g..t..g.....t.....g.....a.....c..c.....a.....................................a.c.........t.g..........g...
390seq          (  363) .....c.tg..t..g.....t.....g.....a.....c..c.....a.....................................a.c.........t.g..........g...
H. felis com    (  400) a.t..c..c..........cc.ttagct.ga.a..g.aa...a....cga.cgtc.tg....g.....atca.............c....tg..t...ctct.gg.c........c.c.
H. pylori co    ( 3016) a....c.a.......a...ccgttagcg.ga.a....aa....tt..cgac.g.c.gg.t..aa.c..ctca..c.....t..........tg..t.gatgc...g.c..t...ca.a...
H. heilmanni    (  571) .....c..c......c.c.ccgt.c..t.aa.a..c.aa..ca....cga.cgcc..g.a..a......tca..c................tg..t...cttt..g.c........c...
```

Figure 1a (1)

```
Cs1seq       (   686) aaagcctatggcaaacgcctagatattccctctggcaacacgctacgcattggggcaggacaaacccgcaaagtgcagttgattcctcttggtggcagtaaaaaagtgattggcatgaac
Kukkaseq     (   528) ..........................................a.....................t..........a..c........c..t.....................
Ds4seq       (   482) ..........................................................t..........a..c........c.....................
2301SEQ      (   481) ..........................................................t..........a..c........c..t...................
390seq       (   483) ..........................................................t..........a..c........c..t...................
H. felis com (   520) ...ag..t.t.............c...g.a.....a.cag..g.g...t...aac.c..gg.ggaaaaa.gt...g.ac.c...gaca.c..c..g.a...gcgca.cta....t.t..t
H. pylori co (  3136) ...a.t.tc..t......t....c...g.gagc..g.cag..g..a.at...a.c.t..cg..gaaaaatcc..ag.a......gaca....c..t.ac.g..g.a.ct....at.t...
H. heilmanni (   691) ..................c...g.t.......c.g.tg.g...t...aac.t..gg..gaaaaa.cc...g.ac.c..cgaca.c.......a....cgca.tta...tt.c...

Cs1seq       (   806) gggcttgtgaataacatcgcggatga------------------------acgccataaacataaagcgcttgacaaggcgaaatctcacggattt-----------------------
Kukkaseq     (   648) ..............t..t.....c..-----------------------.....c........a.....a..a.....------------------------
Ds4seq       (   602) ..............t..t..a.....-----------------------.....c......t.a..a..a..a.....------------------------
2301SEQ      (   601) ..............t..t.....c..-----------------------.....c.....a..a........a.....c------------------------
390seq       (   603) ..............t..t.....c..-----------------------.....c.....a..a........a.....c------------------------
H. felis com (   640) tctt.g...g..cg.caa..c....c-----------------------cgatgg....a.actc.gct.aa.acgc..t...gaaa.a..t...gggtctgtaaactgcggttgtga-
H. pylori co (  3256) .cat.g..tg...gacaa..a..ca.-----------------------cgaaagc...a.a.tt..tt.ac...ga..t...gag.gt..t...catggcgctaaaagcgatgacaac
H. heilmanni (   811) .ct..a..cg..cg.caa..c...c.cgatggcaaaaaactcgccttaaa....gc....g.a...cact...g..ctatc..c.gcggtt.cgac-----------------------

Cs1seq       (   878) --------atcaagtaaggagactc------------ccatgaaaatgaaaaa-------ac---aagaatatgtaaatacctacggacccaccaaaggcgataaagtgcgcttaggaga
Kukkaseq     (   720) --------.............-----------.............-------..---....g.....................c.....................
Ds4seq       (   674) --------.....a.....-----------.............-------..---....g.....................t....c......c.....................
2301SEQ      (   673) --------.....a.....-----------.............-------..---....g.....................c.....................
390seq       (   675) --------.....a.....-----------.............-------..---....g.....................c.....................
H. felis com (   735) --------.g.g.c...a..t.aa.aataaggaaaaa.........a..tttc-------..gaa.........ttc..tg..t..t.....t.cc..g...cgt..ta.ac.c..c..
H. pylori co (  3352) tatgtaaa.a...t.......taag------------aa.......a..tt.gcag----.a---.........ttc..tg..t..t..t..t.c.............a.a..g..c..
H. heilmanni (   907) --------.a...a......a.gga------------ag.ccg.tgaa.....tttctcg.a---.........ttc..tg..t........t.cg.................g..c..

Cs1seq       (   968) taccgatctttgggcagaagtagaacatgactataccacctatggcgaagaacttaaatttggcgcgggtaaaactatccgtgagggtatgggtcagagcaatagccctgatgaaaacac
Kukkaseq     (   810) ..........................................c.....c..t..a.....................................a.....................
Ds4seq       (   764) ..........................t..........g..c.....................................c.................t..a.....................
2301SEQ      (   763) ..........................t..........g..c.....................................................a.....................
390seq       (   765) ..........................t..........g..c.....................................................a.....................
H. felis com (   840) c..t...t.gatctt.....g..g.....t.gc.....t.....t.....ga.c........g.gc.................t..g...a....a.c..........agctctt.tga
H. pylori co (  3453) ...a..ct.gatc..t.................c....tt..........g........c..t.gc........cc.aa.a..a..c...a.c..atct..c.a....agca..g.aga
H. heilmanni (  1004) c..t...c..gatcct......c..........gc.....t............a.c.....c..g.gc..g.....c.....c..t..g.....a..a.c...c.....cagcagcc.tga

Cs1seq       (  1088) cctagatttagtcatcactaacgcgatgattatcgactacaccgggatttacaaagccgacattgggattaaaaacggcaaaatccatggcattggcaaggcaggaaacaaggacatgca
Kukkaseq     (   930) .t.........g.....c.............t.....................................c........t.....................................
Ds4seq       (   884) ...................c.............t.....................................c........t.....................................
2301SEQ      (   883) .t.........g.....c.....................................t.............t.............t..........g..g.....a.....
390seq       (   885) .t.........g.....c.....................................t.............t........t.............t..........g..g.....a.....
H. felis com (   960) at.......g..gc..........cc.c...g.g.....t..g..c.....................g.......g..tgca.................c..t...........
H. pylori co (  3573) gt.g......a.t...........tt.a..cg.g..t.......t.....t.....g..t.....t......g.t.........gc.........t..a.gc..t.....a.......
H. heilmanni (  1124) g..c...c.t........c......c.....g.g..t........c.....................c.....................c..g........a..c..c.....a...c.a..

Cs1seq       (  1208) agatggcgtaagccctcatatggtcgtgggtgtgggcacagaagcactagcaggggaaggtatgattattaccgctgggggaatcgattcacacacccacttcctttctccacaacaatt
Kukkaseq     (  1050) ..........................................................................g.....................c.....................
Ds4seq       (  1004) ..........................................t.....................................g.....................c.....................
2301SEQ      (  1003) .....:.....................................................................g........g.............c.....c.....c.....
390seq       (  1005) ..........................................................................g........g.............c.....c.....c.....
H. felis com (  1080) .........gataa.a..c.ttg...a...cct.ct.....g..tt.g....ct..g..ct.....g.a........t..c......a.g..t.tt.....ta.c.....c.....a.
H. pylori co (  3693) .........t.aaaaca..c.tag...a...cct.ct..t.....ct....c..t.....t....cg.a..g.....t..t..t..ca......t.......a....a..c......a.
H. heilmanni (  1244) .........tt..aacaggc.ctg...a..acct.ct........t..c..t.ct.....ct.....g.......c..t..g.....ca.c....t.......a.......t......a.
```

Figure 1a (2)

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ureYCS1     (  480) hhgkakfdtsitfvskvayengvkeklglerqvlpvkncrnitkkdfkfndktakitvdpktfevfvdgklctskptsqvplaqrytff
ureYkuka    (  480) ...............................k..............................................e..........
ureYDS4     (  480) ...............................k..................n...h.....................a.e..........
ureY2301    (  480) ...............................k..................n...h.....................a.e..........
ureY390     (  480) .............------------------------------------------------------------------------rvss
B felis     (  481) ....n....n.....qa..ka.i..e...d.aap............l....v..h.d.n.e.yk.k....ev...aadels...l.nl.
B pylori    (  481) ......y.an.....qa..dk.i..e....................mq...t..h.e.n.e.yh......ev....ank.s...lfsi.
B heilman   (  480) .........n.....q......ı.he...q.v..............l....v..h.e.n.e.yk.k...nev..haadkls...l.nl.
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Figure 1c (2)

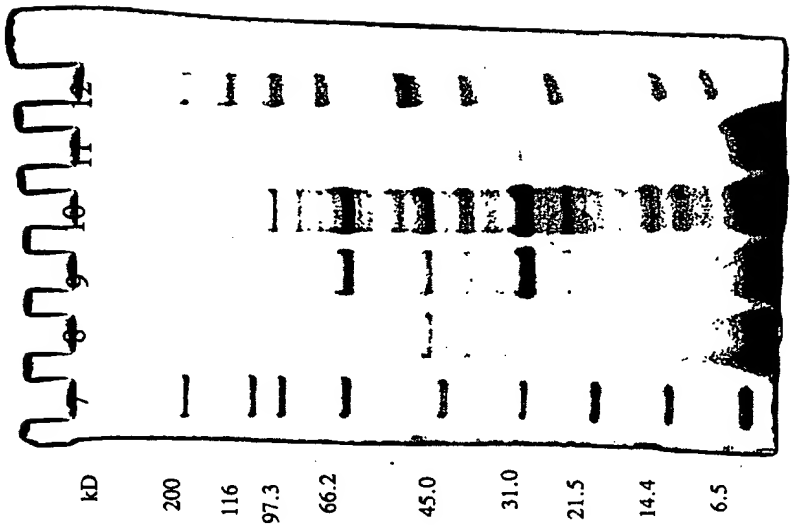

Figure 2

SEQUENCE LISTING

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<120> Helicobacter vaccine

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<400> 1

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Val Lys Leu Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr Ala
  1               5                  10                  15

ggc gaa gtg gct aga aag cgc aaa gca gag ggc tta aag ctc aat caa   96
Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln
             20                  25                  30

ccc gaa gcc att gcc tac att agt gcc cat att atg gac gag gcg cgc   144
Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
         35                  40                  45

cgt ggc aaa aaa acc gtt gct gaa ctt atg gaa gaa tgt atg cac ttt   192
Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe
     50                  55                  60

ttg aaa aaa gat gag gtg atg ccc ggt gtg ggg aat atg gtc cct gat   240
Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
 65                  70                  75                  80
```

```
ttg ggc gta gaa gcc act ttc ccc gat ggc acc aaa ctc gta acc gtg   288
Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
                85                  90                  95

aat tgg ccc att gaa cct gat gaa cac ttt aaa gcc ggt gaa gtg aaa   336
Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
            100                 105                 110

ttt ggc tgt gat aaa gac att gag ctc aac gcg ggt aag gaa gtt acc   384
Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
        115                 120                 125

gag ctt gaa gtt acc aac gaa gga cct aaa tcc ttg cat gtg ggt agc   432
Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
    130                 135                 140

cat ttc cac ttc ttt gaa acc aac aag gca ttg aaa ttc gat cgg gaa   480
His Phe His Phe Phe Glu Thr Asn Lys Ala Leu Lys Phe Asp Arg Glu
145                 150                 155                 160

aaa gcc tat ggc aaa cgc cta gat att ccc tct ggc aac acg cta cgc   528
Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
                165                 170                 175

att ggg gca gga caa acc cgt aaa gtg cag tta atc cct ctt ggc ggt   576
Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
            180                 185                 190

agt aaa aaa gtg att ggc atg aac ggg ctt gtg aat aat att gcg gac   624
Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
        195                 200                 205

gaa cgc cat aaa cac aaa gca cta gac aag gca aaa tct cac gga ttc   672
Glu Arg His Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly Phe
    210                 215                 220

atc aag taa ggagactccc atg aaa atg aaa aaa caa gag tat gta aac   721
Ile Lys                 Met Lys Met Lys Lys Gln Glu Tyr Val Asn
225                             230                 235

acc tac gga ccc acc aca ggc gat aaa gtg cgc tta gga gat acc gat   769
Thr Tyr Gly Pro Thr Thr Gly Asp Lys Val Arg Leu Gly Asp Thr Asp
        240                 245                 250

ctt tgg gca gaa gta gaa cat gac tat acc act tat ggc gaa gag ctc   817
Leu Trp Ala Glu Val Glu His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu
    255                 260                 265
```

```
aaa ttt ggc gcg ggt aaa act atc cgt gag ggt atg ggt cag agc aat   865
Lys Phe Gly Ala Gly Lys Thr Ile Arg Glu Gly Met Gly Gln Ser Asn
270                 275                 280                 285

agc cca gat gaa aac acc tta gat tta gtg atc acc aac gcg atg att   913
Ser Pro Asp Glu Asn Thr Leu Asp Leu Val Ile Thr Asn Ala Met Ile
                290                 295                 300

atc gac tac acc ggg att tat aaa gcc gac att ggt att aaa aat ggc   961
Ile Asp Tyr Thr Gly Ile Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly
            305                 310                 315

aaa atc cat ggt att ggc aag gcg ggg aac aaa gac atg caa gat ggc   1009
Lys Ile His Gly Ile Gly Lys Ala Gly Asn Lys Asp Met Gln Asp Gly
        320                 325                 330

gta agc cct cat atg gtc gtg ggt gtg ggc aca gaa gca cta gca ggg   1057
Val Ser Pro His Met Val Val Gly Val Gly Thr Glu Ala Leu Ala Gly
    335                 340                 345

gaa ggt atg att att acc gct ggg ggg atc gat tcg cac acc cac ttc   1105
Glu Gly Met Ile Ile Thr Ala Gly Gly Ile Asp Ser His Thr His Phe
350                 355                 360                 365

ctc tct ccc caa caa ttc cct acc gct cta gcc aat ggt gtt aca acc   1153
Leu Ser Pro Gln Gln Phe Pro Thr Ala Leu Ala Asn Gly Val Thr Thr
                370                 375                 380

atg ttt gga ggt ggc aca ggt ccg gta gat ggc acg aat gcg acc acc   1201
Met Phe Gly Gly Gly Thr Gly Pro Val Asp Gly Thr Asn Ala Thr Thr
            385                 390                 395

atc act ccg ggc aaa tgg aac ttg cac cgc atg ttg cgc gca gct gaa   1249
Ile Thr Pro Gly Lys Trp Asn Leu His Arg Met Leu Arg Ala Ala Glu
        400                 405                 410

gag tat tct atg aat gtg ggc ttt ttg ggc aaa ggc aat agc tcc agt   1297
Glu Tyr Ser Met Asn Val Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser
    415                 420                 425

aaa aaa caa ctc gta gaa caa gta gaa gcg ggc gcg att ggc ttt aaa   1345
Lys Lys Gln Leu Val Glu Gln Val Glu Ala Gly Ala Ile Gly Phe Lys
430                 435                 440                 445

ttg cat gaa gac tgg ggc aca aca cca agt gcg atc gat cac tgc ttg   1393
Leu His Glu Asp Trp Gly Thr Thr Pro Ser Ala Ile Asp His Cys Leu
                450                 455                 460
```

```
agc gta gca gat gaa tac gat gtg caa gtt tgt atc cac acc gat acg   1441
Ser Val Ala Asp Glu Tyr Asp Val Gln Val Cys Ile His Thr Asp Thr
            465                 470                 475

gtc aat gag gca ggt tat gta gat gac acc cta aat gcg atg aac ggg   1489
Val Asn Glu Ala Gly Tyr Val Asp Asp Thr Leu Asn Ala Met Asn Gly
        480                 485                 490

cgc gcc atc cat gcc tac cac att gag gga gcg ggc gga gga cac tca   1537
Arg Ala Ile His Ala Tyr His Ile Glu Gly Ala Gly Gly Gly His Ser
    495                 500                 505

cct gat gtt atc acc atg gca ggc gag ctc aat att cta ccc tcc tcc   1585
Pro Asp Val Ile Thr Met Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser
510                 515                 520                 525

acc acc ccc act att ccc tat acc att aat acg gtt gca gaa cac tta   1633
Thr Thr Pro Thr Ile Pro Tyr Thr Ile Asn Thr Val Ala Glu His Leu
                530                 535                 540

gac atg ctc atg acc tgc cac cac cta gac aaa cgc atc cgc gag gat   1681
Asp Met Leu Met Thr Cys His His Leu Asp Lys Arg Ile Arg Glu Asp
            545                 550                 555

ctc cag ttt tcc caa agc cgt atc cgc ccc ggc tct att gcc gct gaa   1729
Leu Gln Phe Ser Gln Ser Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu
        560                 565                 570

gat gtg ctc cat gat att ggc gtg atc gcg atg aca agc tcg gat tcg   1777
Asp Val Leu His Asp Ile Gly Val Ile Ala Met Thr Ser Ser Asp Ser
    575                 580                 585

caa gca atg ggg cgc gct ggg gaa gtg att cct aga act tgg caa act   1825
Gln Ala Met Gly Arg Ala Gly Glu Val Ile Pro Arg Thr Trp Gln Thr
590                 595                 600                 605

gca gac aag aat aaa aaa gaa ttt ggt aag ctt cct gaa gat ggt gca   1873
Ala Asp Lys Asn Lys Lys Glu Phe Gly Lys Leu Pro Glu Asp Gly Ala
                610                 615                 620

gat aat gac aac ttc cgc atc aaa cgc tat atc tcc aaa tac acc att   1921
Asp Asn Asp Asn Phe Arg Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile
            625                 630                 635

aat ccc gct ttg acc cat ggc gtg agc gag tat atc ggc tct gtg gaa   1969
Asn Pro Ala Leu Thr His Gly Val Ser Glu Tyr Ile Gly Ser Val Glu
        640                 645                 650
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gag ggc aag atc gcc gac ttg gtg gtg tgg aat cct gct ttc ttt ggt   2017
Glu Gly Lys Ile Ala Asp Leu Val Val Trp Asn Pro Ala Phe Phe Gly
    655                 660                 665

gta aaa ccc aaa atc gtg atc aaa ggc ggt atg gtg gtg ttc tct gaa   2065
Val Lys Pro Lys Ile Val Ile Lys Gly Gly Met Val Val Phe Ser Glu
670                 675                 680                 685

atg ggc gat tct aac gcg tct gtg ccc aca cct cag ccg gtt tat tac   2113
Met Gly Asp Ser Asn Ala Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr
                690                 695                 700

cgc gaa atg ttt ggg cat cac ggc aag gcg aaa ttt gac acc agc atc   2161
Arg Glu Met Phe Gly His His Gly Lys Ala Lys Phe Asp Thr Ser Ile
            705                 710                 715

act ttt gtt tcc aaa gtc gcc tat gaa aat ggc gtg aaa gaa aaa cta   2209
Thr Phe Val Ser Lys Val Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu
        720                 725                 730

ggc tta gag cgc aag gtg cta ccc gtg aaa aac tgc cgc aac atc act   2257
Gly Leu Glu Arg Lys Val Leu Pro Val Lys Asn Cys Arg Asn Ile Thr
    735                 740                 745

aag aaa gac ttc aaa ttc aac aac aag acg gcg cat atc act gtc gat   2305
Lys Lys Asp Phe Lys Phe Asn Asn Lys Thr Ala His Ile Thr Val Asp
750                 755                 760                 765

cct aaa acc ttc gag gtc ttt gta gat ggc aaa ctc tgc acc tct aaa   2353
Pro Lys Thr Phe Glu Val Phe Val Asp Gly Lys Leu Cys Thr Ser Lys
                770                 775                 780

ccc gcc tct gaa gtg cct cta gcc caa cgc tac act ttc ttc tag       2398
Pro Ala Ser Glu Val Pro Leu Ala Gln Arg Tyr Thr Phe Phe
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gcacaat                                                          2405
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20 25 30

Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
35 40 45

Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe
50 55 60

Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
65 70 75 80

Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
85 90 95

Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
100 105 110

Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
115 120 125

Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
130 135 140

His Phe His Phe Phe Glu Thr Asn Lys Ala Leu Lys Phe Asp Arg Glu
145 150 155 160

Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
165 170 175

Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
180 185 190

Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
195 200 205

Glu Arg His Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly Phe
210 215 220

Ile Lys
225

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 1               5                  10                  15

Gly Asp Lys Val Arg Leu Gly Asp Thr Asp Leu Trp Ala Glu Val Glu
            20                  25                  30

His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys
        35                  40                  45

Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp Glu Asn Thr
    50                  55                  60

Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr Thr Gly Ile
65                  70                  75                  80

Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly
                85                  90                  95

Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val
            100                 105                 110

Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met Ile Ile Thr
        115                 120                 125

Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro Gln Gln Phe
    130                 135                 140

Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly Gly Gly Thr
145                 150                 155                 160

Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp
                165                 170                 175

Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val
            180                 185                 190

Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln Leu Val Glu
        195                 200                 205

Gln Val Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu Asp Trp Gly
    210                 215                 220

Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala Asp Glu Tyr
225                 230                 235                 240

Asp Val Gln Val Cys Ile His Thr Asp Thr Val Asn Glu Ala Gly Tyr
```

245 250 255

Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr
260 265 270

His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met
275 280 285

Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro
290 295 300

Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys
305 310 315 320

His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser
325 330 335

Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Ile
340 345 350

Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala
355 360 365

Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys Asn Lys Lys
370 375 380

Glu Phe Gly Lys Leu Pro Glu Asp Gly Ala Asp Asn Asp Asn Phe Arg
385 390 395 400

Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His
405 410 415

Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp
420 425 430

Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val
435 440 445

Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala
450 455 460

Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His
465 470 475 480

His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Val Ser Lys Val
485 490 495

Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu Gly Leu Glu Arg Lys Val

```
            500                 505                 510

Leu Pro Val Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp Phe Lys Phe
        515                 520                 525

Asn Asn Lys Thr Ala His Ile Thr Val Asp Pro Lys Thr Phe Glu Val
    530                 535                 540

Phe Val Asp Gly Lys Leu Cys Thr Ser Lys Pro Ala Ser Glu Val Pro
545                 550                 555                 560

Leu Ala Gln Arg Tyr Thr Phe Phe
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     1               5                  10                  15

gcg ggc gaa gtg gct aga aag cgc aaa gca gag ggc tta aag ctc aat   95
Ala Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn
                20                  25                  30

caa ccc gaa gcc att gcc tac att agt gcc cat att atg gac gag gcg   143
Gln Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala
            35                  40                  45

cgc cgt ggc aaa aaa acc gtt gct gaa ctt atg gaa gaa tgt atg cac   191
Arg Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His
        50                  55                  60

ttt ttg aaa aaa gat gag gtg atg ccc ggt gtg ggg aat atg gtc cct   239
Phe Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro
```

```
     65                  70                  75

gat ttg ggc gta gaa gcc act ttc ccc gat ggc acc aaa ctc gta acc   287
Asp Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr
 80                  85                  90                  95

gtg aat tgg ccc att gaa cct gat gaa cac ttt aaa gcc ggt gaa gtg   335
Val Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val
                100                 105                 110

aaa ttt ggc tgt gat aaa gac att gag ctc aac gtg ggt aag gaa gtt   383
Lys Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Val Gly Lys Glu Val
            115                 120                 125

acc gag ctt gaa gtt acc aac gaa gga cct aaa tcc ttg cat gtg ggt   431
Thr Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly
        130                 135                 140

agc cat ttc cac ttc ttt gaa acc aac aag gca ttg aaa ttc gat cgg   479
Ser His Phe His Phe Phe Glu Thr Asn Lys Ala Leu Lys Phe Asp Arg
    145                 150                 155

gaa aaa gcc tat ggc aaa cgc cta gat att ccc tct ggc aac acg cta   527
Glu Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu
160                 165                 170                 175

cgc att ggg gca gga caa acc cgt aaa gtg cag tta atc cct ctt ggc   575
Arg Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly
                180                 185                 190

ggt agt aaa aaa gtg att ggc atg aac ggg ctt gtg aat aat att gcg   623
Gly Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala
            195                 200                 205

gac gaa cgc cat aaa cac aaa gca cta gac aag gca aaa tct cac gga   671
Asp Glu Arg His Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly
        210                 215                 220

ttc atc aag taa ggagactccc atg aaa atg aaa aaa caa gag tat gta   720
Phe Ile Lys                 Met Lys Met Lys Lys Gln Glu Tyr Val
    225                             230                 235

aac acc tac gga ccc acc aca ggc gat aaa gtg cgc tta gga gat acc   768
Asn Thr Tyr Gly Pro Thr Thr Gly Asp Lys Val Arg Leu Gly Asp Thr
            240                 245                 250

gat ctt tgg gca gaa gta gaa cat gac tat acc act tat ggc gaa gag   816
Asp Leu Trp Ala Glu Val Glu His Asp Tyr Thr Thr Tyr Gly Glu Glu
```

```
        255                 260                 265

ctc aaa ttt ggc gcg ggt aaa act atc cgt gag ggt atg ggt cag agc   864
Leu Lys Phe Gly Ala Gly Lys Thr Ile Arg Glu Gly Met Gly Gln Ser
    270                 275                 280

aat agc cca gat gaa aac acc tta gat tta gtg atc acc aac gcg atg   912
Asn Ser Pro Asp Glu Asn Thr Leu Asp Leu Val Ile Thr Asn Ala Met
285                 290                 295                 300

att atc gac tac acc ggg att tat aaa gcc gac att ggt att aaa aat   960
Ile Ile Asp Tyr Thr Gly Ile Tyr Lys Ala Asp Ile Gly Ile Lys Asn
                305                 310                 315

ggc aaa atc cat ggt att ggc aag gcg ggg aac aaa gac atg caa gat  1008
Gly Lys Ile His Gly Ile Gly Lys Ala Gly Asn Lys Asp Met Gln Asp
            320                 325                 330

ggc gta agc cct cat atg gtc gtg ggt gtg ggc aca gaa gca cta gca  1056
Gly Val Ser Pro His Met Val Val Gly Val Gly Thr Glu Ala Leu Ala
        335                 340                 345

ggg gaa ggt atg att att acc gct ggg ggg atc gat tcg cac acc cac  1104
Gly Glu Gly Met Ile Ile Thr Ala Gly Gly Ile Asp Ser His Thr His
    350                 355                 360

ttc ctc tct ccc caa caa ttc cct acc gct cta gcc aat ggt gtt aca  1152
Phe Leu Ser Pro Gln Gln Phe Pro Thr Ala Leu Ala Asn Gly Val Thr
365                 370                 375                 380

acc atg ttt gga ggt ggc aca ggt ccg gta gat ggc acg aat gcg acc  1200
Thr Met Phe Gly Gly Gly Thr Gly Pro Val Asp Gly Thr Asn Ala Thr
                385                 390                 395

acc atc act ccg ggc aaa tgg aac ttg cac cgc atg ttg cgc gca gct  1248
Thr Ile Thr Pro Gly Lys Trp Asn Leu His Arg Met Leu Arg Ala Ala
            400                 405                 410

gaa gag tat tct atg aat gta ggc ttt ttg ggc aaa ggc aat agt tct  1296
Glu Glu Tyr Ser Met Asn Val Gly Phe Leu Gly Lys Gly Asn Ser Ser
        415                 420                 425

agc aaa aaa caa ctt gta gaa caa gta gaa gcg ggc gcg att ggc ttt  1344
Ser Lys Lys Gln Leu Val Glu Gln Val Glu Ala Gly Ala Ile Gly Phe
    430                 435                 440

aaa ttg cat gaa gac tgg ggc aca aca cca agt gcg atc gat cac tgc  1392
Lys Leu His Glu Asp Trp Gly Thr Thr Pro Ser Ala Ile Asp His Cys
```

```
445                 450                 455                 460

ttg agc gtg gca gat gaa tac gat gtg caa gtt tgt atc cac acc gat   1440
Leu Ser Val Ala Asp Glu Tyr Asp Val Gln Val Cys Ile His Thr Asp
                465                 470                 475

acg gtc aat gag gca ggt tat gtg gat gac acc cta aat gca atg aac   1488
Thr Val Asn Glu Ala Gly Tyr Val Asp Asp Thr Leu Asn Ala Met Asn
            480                 485                 490

ggg cgc gcc atc cat gcc tac cac att gag gga gcg ggc gga gga cac   1536
Gly Arg Ala Ile His Ala Tyr His Ile Glu Gly Ala Gly Gly Gly His
        495                 500                 505

tca cct gat gtt atc acc atg gca ggc gag ctc aat att cta ccc tcc   1584
Ser Pro Asp Val Ile Thr Met Ala Gly Glu Leu Asn Ile Leu Pro Ser
    510                 515                 520

tcc acc acc ccc act att ccc tat acc att aat acg gtt gca gaa cac   1632
Ser Thr Thr Pro Thr Ile Pro Tyr Thr Ile Asn Thr Val Ala Glu His
525                 530                 535                 540

tta gac atg ctc atg acc tgc cac cac cta gat aag cgc atc cgc gag   1680
Leu Asp Met Leu Met Thr Cys His His Leu Asp Lys Arg Ile Arg Glu
                545                 550                 555

gat tta caa ttt tct caa agc cgt atc cgc ccc gga tct att gcc gct   1728
Asp Leu Gln Phe Ser Gln Ser Arg Ile Arg Pro Gly Ser Ile Ala Ala
            560                 565                 570

gag gat gtg ctc cat gat att ggc gtg atc gcg atg act agc tcc gat   1776
Glu Asp Val Leu His Asp Ile Gly Val Ile Ala Met Thr Ser Ser Asp
        575                 580                 585

tcg caa gca atg ggg cgc gct ggg gaa gtg att cct aga act tgg caa   1824
Ser Gln Ala Met Gly Arg Ala Gly Glu Val Ile Pro Arg Thr Trp Gln
    590                 595                 600

act gca gat aag aat aaa aaa gaa ttt ggt aag ctt cct gaa gat ggt   1872
Thr Ala Asp Lys Asn Lys Lys Glu Phe Gly Lys Leu Pro Glu Asp Gly
605                 610                 615                 620

gca gat aac gac aac ttc cgc atc aaa cgc tat atc tcc aaa tac acc   1920
Ala Asp Asn Asp Asn Phe Arg Ile Lys Arg Tyr Ile Ser Lys Tyr Thr
                625                 630                 635

att aat ccc gct ttg acc cat ggc gtg agc gag tat atc ggc tct gtg   1968
Ile Asn Pro Ala Leu Thr His Gly Val Ser Glu Tyr Ile Gly Ser Val
```

```
            640                 645                 650

gaa gag ggc aag atc gcc gac ttg gtg gtg tgg aat cct gcc ttt ttt   2016
Glu Glu Gly Lys Ile Ala Asp Leu Val Val Trp Asn Pro Ala Phe Phe
        655                 660                 665

ggc gtg aaa cct aag att gtg att aaa ggt ggc atg gtg gtc ttc tct   2064
Gly Val Lys Pro Lys Ile Val Ile Lys Gly Gly Met Val Val Phe Ser
    670                 675                 680

gaa atg ggc gat tct aac gcg tcc gtg ccc acg cct cag ccg gtt tat   2112
Glu Met Gly Asp Ser Asn Ala Ser Val Pro Thr Pro Gln Pro Val Tyr
685                 690                 695                 700

tac cgc gaa atg ttt ggg cac cac ggc aag gcg aaa ttt gac acc agc   2160
Tyr Arg Glu Met Phe Gly His His Gly Lys Ala Lys Phe Asp Thr Ser
                705                 710                 715

atc act ttt cgt gtc tca agc gg                                   2183
Ile Thr Phe Arg Val Ser Ser
            720
```

<210> 5
<211> 226
<212> PRT
<213> Helicobacter felis

<400> 5

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Val Lys Leu Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr Ala
  1               5                  10                  15

Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln
             20                  25                  30

Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
         35                  40                  45

Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe
     50                  55                  60

Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
 65                  70                  75                  80

Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
                 85                  90                  95

Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
```

```
            100                 105                 110

Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Val Gly Lys Glu Val Thr
        115                 120                 125

Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
    130                 135                 140

His Phe His Phe Phe Glu Thr Asn Lys Ala Leu Lys Phe Asp Arg Glu
145                 150                 155                 160

Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
                165                 170                 175

Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
            180                 185                 190

Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
        195                 200                 205

Glu Arg His Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly Phe
    210                 215                 220

Ile Lys
225
```

<210> 6
<211> 496
<212> PRT
<213> Helicobacter felis

<400> 6

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Met Lys Met Lys Lys Gln Glu Tyr Val Asn Thr Tyr Gly Pro Thr Thr
  1               5                  10                  15

Gly Asp Lys Val Arg Leu Gly Asp Thr Asp Leu Trp Ala Glu Val Glu
            20                  25                  30

His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys
        35                  40                  45

Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp Glu Asn Thr
    50                  55                  60

Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr Thr Gly Ile
65                  70                  75                  80
```

```
Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly
                85                  90                  95

Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val
            100                 105                 110

Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met Ile Ile Thr
        115                 120                 125

Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro Gln Gln Phe
    130                 135                 140

Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly Gly Gly Thr
145                 150                 155                 160

Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp
                165                 170                 175

Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val
            180                 185                 190

Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln Leu Val Glu
        195                 200                 205

Gln Val Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu Asp Trp Gly
    210                 215                 220

Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala Asp Glu Tyr
225                 230                 235                 240

Asp Val Gln Val Cys Ile His Thr Asp Thr Val Asn Glu Ala Gly Tyr
                245                 250                 255

Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr
            260                 265                 270

His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met
        275                 280                 285

Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro
    290                 295                 300

Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys
305                 310                 315                 320

His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser
                325                 330                 335
```

```
Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Ile
            340                 345                 350

Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala
        355                 360                 365

Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys Asn Lys Lys
    370                 375                 380

Glu Phe Gly Lys Leu Pro Glu Asp Gly Ala Asp Asn Asp Asn Phe Arg
385                 390                 395                 400

Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His
                405                 410                 415

Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp
            420                 425                 430

Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val
        435                 440                 445

Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala
    450                 455                 460

Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His
465                 470                 475                 480

His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Arg Val Ser Ser
                485                 490                 495
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<210> 7
<211> 2883
<212> DNA
<213> Helicobacter felis

<220>
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<222> (206)..(886)

<220>
<221> CDS
<222> (897)..(2603)

<400> 7
rggragattt tccarcactt caagcacata ttgatcctgt gttgtgggtg gtaaattrcr 60

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acttgttaat rctattatta atttttaat aattacttat tatcatatat aataatatta 120

ttacttatat taaaaagtta ataaaaagta acgaaattag gactataatc ccattgcctt 180

taaaatttaa cacaaggagt aatag gtg aaa ctc aca ccc aaa gag caa gaa   232
                            Val Lys Leu Thr Pro Lys Glu Gln Glu
                              1               5

aag ttc ttg tta tat tat gcg ggc gaa gtg gct aga aag cgc aaa gca   280
Lys Phe Leu Leu Tyr Tyr Ala Gly Glu Val Ala Arg Lys Arg Lys Ala
 10                  15                  20                  25

gag ggc tta aag ctc aac caa ccc gaa gcc att gct tac att agt gcc   328
Glu Gly Leu Lys Leu Asn Gln Pro Glu Ala Ile Ala Tyr Ile Ser Ala
                 30                  35                  40

cat att atg gac gaa gcg cgc cgt gga aaa aaa acc gtt gcc cag ctt   376
His Ile Met Asp Glu Ala Arg Arg Gly Lys Lys Thr Val Ala Gln Leu
             45                  50                  55

atg gaa gag tgc atg cac ttt ttg aaa aaa gat gaa gta atg ccc ggg   424
Met Glu Glu Cys Met His Phe Leu Lys Lys Asp Glu Val Met Pro Gly
         60                  65                  70

gtg ggt aat atg gtt ccc gat cta ggt gta gaa gcc acc ttt cct gat   472
Val Gly Asn Met Val Pro Asp Leu Gly Val Glu Ala Thr Phe Pro Asp
     75                  80                  85

ggt acg aaa ctt gta act gtg aat tgg ccc atc gaa cca gat gag cac   520
Gly Thr Lys Leu Val Thr Val Asn Trp Pro Ile Glu Pro Asp Glu His
 90                  95                 100                 105

ttc aaa gcg ggc gaa gtg aaa ttt ggt tgc gat aaa gac atc gag ctc   568
Phe Lys Ala Gly Glu Val Lys Phe Gly Cys Asp Lys Asp Ile Glu Leu
                110                 115                 120

aat gca ggc aaa gaa gta acc gaa ctt gag gtt act aat gaa ggg cct   616
Asn Ala Gly Lys Glu Val Thr Glu Leu Glu Val Thr Asn Glu Gly Pro
            125                 130                 135

aaa tcc ttg cat gtg ggt agc cat ttc cac ttc ttt gaa gct aac aag   664
Lys Ser Leu His Val Gly Ser His Phe His Phe Phe Glu Ala Asn Lys
        140                 145                 150

gca cta aaa ttc gat cgt gaa aaa gcc tat ggc aaa cgc cta gat att   712
Ala Leu Lys Phe Asp Arg Glu Lys Ala Tyr Gly Lys Arg Leu Asp Ile
    155                 160                 165
```

```
ccc tct ggc aac acg cta cgc att ggg gca gga caa acc cgc aaa gtg   760
Pro Ser Gly Asn Thr Leu Arg Ile Gly Ala Gly Gln Thr Arg Lys Val
170                 175                 180                 185

cag ttg att cct ctt ggt ggc agt aaa aaa gtg att ggc atg aac ggg   808
Gln Leu Ile Pro Leu Gly Gly Ser Lys Lys Val Ile Gly Met Asn Gly
                190                 195                 200

ctt gtg aat aac atc gcg gat gaa cgc cat aaa cat aaa gcg ctt gac   856
Leu Val Asn Asn Ile Ala Asp Glu Arg His Lys His Lys Ala Leu Asp
            205                 210                 215

aag gcg aaa tct cac gga ttt atc aag taa ggagactccc atg aaa atg    905
Lys Ala Lys Ser His Gly Phe Ile Lys                 Met Lys Met
        220                 225                             230

aaa aaa caa gaa tat gta aat acc tac gga ccc acc aaa ggc gat aaa   953
Lys Lys Gln Glu Tyr Val Asn Thr Tyr Gly Pro Thr Lys Gly Asp Lys
                235                 240                 245

gtg cgc tta gga gat acc gat ctt tgg gca gaa gta gaa cat gac tat   1001
Val Arg Leu Gly Asp Thr Asp Leu Trp Ala Glu Val Glu His Asp Tyr
            250                 255                 260

acc acc tat ggc gaa gaa ctt aaa ttt ggc gcg ggt aaa act atc cgt   1049
Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys Thr Ile Arg
        265                 270                 275

gag ggt atg ggt cag agc aat agc cct gat gaa aac acc cta gat tta   1097
Glu Gly Met Gly Gln Ser Asn Ser Pro Asp Glu Asn Thr Leu Asp Leu
    280                 285                 290

gtc atc act aac gcg atg att atc gac tac acc ggg att tac aaa gcc   1145
Val Ile Thr Asn Ala Met Ile Ile Asp Tyr Thr Gly Ile Tyr Lys Ala
295                 300                 305                 310

gac att ggg att aaa aac ggc aaa atc cat ggc att ggc aag gca gga   1193
Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly Lys Ala Gly
                315                 320                 325

aac aag gac atg caa gat ggc gta agc cct cat atg gtc gtg ggt gtg   1241
Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val Val Gly Val
            330                 335                 340

ggc aca gaa gca cta gca ggg gaa ggt atg att att acc gct ggg gga   1289
Gly Thr Glu Ala Leu Ala Gly Glu Gly Met Ile Ile Thr Ala Gly Gly
        345                 350                 355
```

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atc gat tca cac acc cac ttc ctt tct cca caa caa ttc cct acc gct   1337
Ile Asp Ser His Thr His Phe Leu Ser Pro Gln Gln Phe Pro Thr Ala
    360                 365                 370

cta gcc aat ggc gtt aca acc atg ttt gga ggc ggc aca ggt cct gta   1385
Leu Ala Asn Gly Val Thr Thr Met Phe Gly Gly Gly Thr Gly Pro Val
375                 380                 385                 390

gat ggc acg aat gcg act act atc act ccg ggc aaa tgg aac ttg cac   1433
Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp Asn Leu His
                395                 400                 405

cgc atg ttg cgc gca gca gaa gag tat tct atg aat gtg ggc ttt ttg   1481
Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val Gly Phe Leu
            410                 415                 420

ggc aaa ggc aat agc tct agc aaa aaa caa ctt gta gaa caa gta gaa   1529
Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln Leu Val Glu Gln Val Glu
        425                 430                 435

gcg ggc gcg att ggt ttt aaa ttg cat gaa gac tgg ggc aca aca cca   1577
Ala Gly Ala Ile Gly Phe Lys Leu His Glu Asp Trp Gly Thr Thr Pro
    440                 445                 450

agt gcg atc gat cac tgc ttg agc gtg gca gat gaa tac gat gtg caa   1625
Ser Ala Ile Asp His Cys Leu Ser Val Ala Asp Glu Tyr Asp Val Gln
455                 460                 465                 470

gtt tgt atc cac acc gat aca gtc aat gag gca ggt tat gta gat gac   1673
Val Cys Ile His Thr Asp Thr Val Asn Glu Ala Gly Tyr Val Asp Asp
                475                 480                 485

acc cta aat gca atg aac ggg cgc gcc atc cat gcc tac cac att gag   1721
Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr His Ile Glu
            490                 495                 500

gga gcg ggt gga gga cac tca cct gat gtt atc acc atg gca ggc gag   1769
Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met Ala Gly Glu
        505                 510                 515

ctc aat att cta ccc tcc tcc acc acc ccc act att ccc tat acc att   1817
Leu Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro Tyr Thr Ile
    520                 525                 530

aat acg gtt gca gaa cac tta gac atg ctc atg aca tgc cac cac cta   1865
Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys His His Leu
535                 540                 545                 550
```

```
gac aaa cgc atc cgc gag gat tta caa ttt tct caa agc cgt atc cgc   1913
Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser Arg Ile Arg
                555                 560                 565

ccc ggc tct atc gcg gct gaa gat gtg ctc cat gat atg ggt gtg atc   1961
Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Met Gly Val Ile
            570                 575                 580

gcg atg aca agc tcg gat tcg caa gca atg ggg cgt gca ggc gaa gtg   2009
Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala Gly Glu Val
        585                 590                 595

att cct cga act tgg cag act gcg gat aag aat aaa aaa gaa ttt ggt   2057
Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys Asn Lys Lys Glu Phe Gly
    600                 605                 610

aag ctt cct gaa gat ggc aaa gat aac gat aat ttc cgc att aag cgc   2105
Lys Leu Pro Glu Asp Gly Lys Asp Asn Asp Asn Phe Arg Ile Lys Arg
615                 620                 625                 630

tac atc tcc aaa tac act atc aac ccc gct ttg acc cac ggc gtg agc   2153
Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His Gly Val Ser
                635                 640                 645

gag tat atc ggc tct gtg gaa gag ggc aag atc gcc gac ttg gtg gtg   2201
Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp Leu Val Val
            650                 655                 660

tgg aat cct gcc ttt ttt ggc gta aaa ccc aaa atc gtg atc aaa ggc   2249
Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val Ile Lys Gly
        665                 670                 675

ggt atg gtg gtc ttc tct gaa atg ggc gat tct aac gcg tct gtg ccc   2297
Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala Ser Val Pro
    680                 685                 690

act ccc caa ccg gtt tat tac cgc gaa atg ttt ggg cat cac ggc aag   2345
Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His His Gly Lys
695                 700                 705                 710

gcg aaa ttt gac acc agc atc act ttt gtt tcc aaa gtc gcc tat gaa   2393
Ala Lys Phe Asp Thr Ser Ile Thr Phe Val Ser Lys Val Ala Tyr Glu
                715                 720                 725

aat ggc gtg aaa gaa aag ctg ggc tta gag cgc caa gtt cta ccg gtc   2441
Asn Gly Val Lys Glu Lys Leu Gly Leu Glu Arg Gln Val Leu Pro Val
            730                 735                 740
```

```
aaa aac tgc cgt aac atc acc aag aaa gac ttc aag ttc aac gac aaa   2489
Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp Phe Lys Phe Asn Asp Lys
        745                 750                 755

acg gca aaa atc acc gtc gat ccg aaa acc ttc gag gtc ttt gta gat   2537
Thr Ala Lys Ile Thr Val Asp Pro Lys Thr Phe Glu Val Phe Val Asp
    760                 765                 770

ggc aaa ctc tgc acc tct aaa ccc acc tcg caa gtg cct cta gcc cag   2585
Gly Lys Leu Cys Thr Ser Lys Pro Thr Ser Gln Val Pro Leu Ala Gln
775                 780                 785                 790

cgc tac act ttc ttc tag gcacaatgcc ccctttgggg gcaggttatt          2633
Arg Tyr Thr Phe Phe
                795

ttaggaatct tcatcaaacg cacctgcaat cggtcttgcg tgtgcgatcg tgtcgcttta 2693

aaacaacttt tcatctttaa gcaatcgcca tttttaatta atttaattct tataattaat 2753

attatattat gccccctcat ttttaaagga gaattatgcg taggtctttg gtattgctat 2813

gtgggggttg tttggtgctg ggcgcaaagg gtattgaaac ccatcgcctc aaaaaagtag 2873

aagccacagg                                                        2883
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<210> 8
<211> 226
<212> PRT
<213> Helicobacter felis

<400> 8

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Val Lys Leu Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr Ala
  1               5                  10                  15

Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln
             20                  25                  30

Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
         35                  40                  45

Arg Gly Lys Lys Thr Val Ala Gln Leu Met Glu Glu Cys Met His Phe
     50                  55                  60

Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
 65                  70                  75                  80
```

Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
85 90 95

Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
100 105 110

Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
115 120 125

Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
130 135 140

His Phe His Phe Phe Glu Ala Asn Lys Ala Leu Lys Phe Asp Arg Glu
145 150 155 160

Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
165 170 175

Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
180 185 190

Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
195 200 205

Glu Arg His Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly Phe
210 215 220

Ile Lys
225

<210> 9
<211> 568
<212> PRT
<213> Helicobacter felis

<400> 9
Met Lys Met Lys Lys Gln Glu Tyr Val Asn Thr Tyr Gly Pro Thr Lys
1 5 10 15

Gly Asp Lys Val Arg Leu Gly Asp Thr Asp Leu Trp Ala Glu Val Glu
20 25 30

His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys
35 40 45

Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp Glu Asn Thr
50 55 60

```
Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr Thr Gly Ile
 65                  70                  75                  80

Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly
                85                  90                  95

Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val
            100                 105                 110

Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met Ile Ile Thr
        115                 120                 125

Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro Gln Gln Phe
    130                 135                 140

Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly Gly Gly Thr
145                 150                 155                 160

Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp
                165                 170                 175

Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val
            180                 185                 190

Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln Leu Val Glu
        195                 200                 205

Gln Val Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu Asp Trp Gly
    210                 215                 220

Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala Asp Glu Tyr
225                 230                 235                 240

Asp Val Gln Val Cys Ile His Thr Asp Thr Val Asn Glu Ala Gly Tyr
                245                 250                 255

Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr
            260                 265                 270

His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met
        275                 280                 285

Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro
    290                 295                 300

Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys
305                 310                 315                 320
```

His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser
325 330 335

Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Met
340 345 350

Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala
355 360 365

Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys Asn Lys Lys
370 375 380

Glu Phe Gly Lys Leu Pro Glu Asp Gly Lys Asp Asn Asp Asn Phe Arg
385 390 395 400

Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His
405 410 415

Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp
420 425 430

Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val
435 440 445

Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala
450 455 460

Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His
465 470 475 480

His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Val Ser Lys Val
485 490 495

Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu Gly Leu Glu Arg Gln Val
500 505 510

Leu Pro Val Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp Phe Lys Phe
515 520 525

Asn Asp Lys Thr Ala Lys Ile Thr Val Asp Pro Lys Thr Phe Glu Val
530 535 540

Phe Val Asp Gly Lys Leu Cys Thr Ser Lys Pro Thr Ser Gln Val Pro
545 550 555 560

Leu Ala Gln Arg Tyr Thr Phe Phe
565

<210> 10
<211> 2407
<212> DNA
<213> Helicobacter felis

<220>
<221> CDS
<222> (2)..(682)

<220>
<221> CDS
<222> (693)..(2399)

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c gtg aaa ctc aca ccc aaa gag caa gaa aag ttc ttg tta tat tat gcg 49
  Val Lys Leu Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr Ala
    1   5   10   15

ggc gaa gtg gct aga aag cgc aaa gcg gag ggc tta aag ctc aac caa   97
Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln
            20   25   30

ccc gaa gcc att gcc tac att agt gcc cat att atg gac gag gcg cgc   145
Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
         35   40   45

cgt ggc aaa aag acc gtt gcg gaa ctt atg gaa gag tgt atg cac ttt   193
Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe
     50   55   60

ttg aaa aaa gac gag gtg atg ccc ggt gtg ggg aat atg gtc cct gat   241
Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
 65   70   75   80

tta ggc gtg gaa gct act ttt ccc gat ggc acc aaa ctc gta acc gtg   289
Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
                85   90   95

aat tgg ccc atc gaa ccc gat gaa cac ttc aaa gcg ggc gaa gtc aaa   337
Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
            100   105   110

ttt ggc tgt gat aaa gac att gaa ctc aac gca ggt aag gaa gtt acc   385
Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
        115   120   125

```
gaa cta gaa gtt acc aac gaa gga cct aaa tcc ttg cat gtg ggt agc   433
Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
    130                 135                 140

cat ttc cac ttc ttt gaa gcc aac aag gca ttg aaa ttc gat cgg gaa   481
His Phe His Phe Phe Glu Ala Asn Lys Ala Leu Lys Phe Asp Arg Glu
145                 150                 155                 160

aaa gcc tat ggc aaa cgc cta gat att ccc tct ggc aac acg cta cgc   529
Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
                165                 170                 175

att ggg gca gga caa acc cgt aaa gtg cag tta atc cct ctt ggc ggc   577
Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
            180                 185                 190

agt aaa aaa gtg att ggc atg aac ggg ctt gtg aat aat att gca gat   625
Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
        195                 200                 205

gaa cgc cat aaa cac aaa gcg tta gaa aaa gca aaa tct cac gga ttt   673
Glu Arg His Lys His Lys Ala Leu Glu Lys Ala Lys Ser His Gly Phe
    210                 215                 220

atc aaa taa ggagactccc atg aaa atg aaa aaa caa gag tat gta aat   722
Ile Lys                 Met Lys Met Lys Lys Gln Glu Tyr Val Asn
225                             230                 235

acc tac gga cct acc aca ggc gac aaa gtg cgc tta gga gat acc gat   770
Thr Tyr Gly Pro Thr Thr Gly Asp Lys Val Arg Leu Gly Asp Thr Asp
        240                 245                 250

ctt tgg gca gaa gta gaa cat gac tat acc act tat ggc gaa gag ctc   818
Leu Trp Ala Glu Val Glu His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu
    255                 260                 265

aaa ttt ggc gcg ggt aaa act atc cgt gag ggc atg ggt cag agc aat   866
Lys Phe Gly Ala Gly Lys Thr Ile Arg Glu Gly Met Gly Gln Ser Asn
270                 275                 280                 285

agt cca gat gaa aac acc cta gat tta gtc atc acc aac gcg atg att   914
Ser Pro Asp Glu Asn Thr Leu Asp Leu Val Ile Thr Asn Ala Met Ile
                290                 295                 300

att gac tac acc ggg att tac aaa gcc gac att ggc att aaa aat ggc   962
Ile Asp Tyr Thr Gly Ile Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly
            305                 310                 315
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aaa atc cat ggc att ggc aag gca gga aac aag gac atg caa gat ggc   1010
Lys Ile His Gly Ile Gly Lys Ala Gly Asn Lys Asp Met Gln Asp Gly
        320                 325                 330

gta agc cct cat atg gtc gtg ggt gtg ggc aca gaa gca tta gca ggg   1058
Val Ser Pro His Met Val Val Gly Val Gly Thr Glu Ala Leu Ala Gly
    335                 340                 345

gaa ggt atg att att acc gct ggg ggg atc gat tca cac acc cac ttc   1106
Glu Gly Met Ile Ile Thr Ala Gly Gly Ile Asp Ser His Thr His Phe
350                 355                 360                 365

ctc tct cca caa caa ttc cct acc gct cta gcc aat ggc gtt aca acc   1154
Leu Ser Pro Gln Gln Phe Pro Thr Ala Leu Ala Asn Gly Val Thr Thr
                370                 375                 380

atg ttt ggc ggt ggc aca ggt ccg gta gat ggc acg aat gcg act acc   1202
Met Phe Gly Gly Gly Thr Gly Pro Val Asp Gly Thr Asn Ala Thr Thr
            385                 390                 395

atc act ccg ggc aaa tgg aac ttg cac cgc atg ttg cgc gca gct gaa   1250
Ile Thr Pro Gly Lys Trp Asn Leu His Arg Met Leu Arg Ala Ala Glu
        400                 405                 410

gag tat tct atg aat gtg ggc ttt ttg ggc aaa ggc aat agc tcc agt   1298
Glu Tyr Ser Met Asn Val Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser
    415                 420                 425

aaa aaa caa ctt gta gaa caa ata gaa gcg ggc gcg atc ggc ttt aaa   1346
Lys Lys Gln Leu Val Glu Gln Ile Glu Ala Gly Ala Ile Gly Phe Lys
430                 435                 440                 445

ttg cat gaa gac tgg ggc aca act cca agt gca atc gat cac tgc ttg   1394
Leu His Glu Asp Trp Gly Thr Thr Pro Ser Ala Ile Asp His Cys Leu
                450                 455                 460

agc gta gca gat gaa tac gat gtg caa gtt tgt atc cac acc gat acg   1442
Ser Val Ala Asp Glu Tyr Asp Val Gln Val Cys Ile His Thr Asp Thr
            465                 470                 475

gtc aat gag gca ggt tat gta gat gac acc ctg aat gcg atg aac ggg   1490
Val Asn Glu Ala Gly Tyr Val Asp Asp Thr Leu Asn Ala Met Asn Gly
        480                 485                 490

cgc gcc atc cat gcc tac cac att gag gga gcg ggc gga gga cac tca   1538
Arg Ala Ile His Ala Tyr His Ile Glu Gly Ala Gly Gly Gly His Ser
    495                 500                 505
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cct gat gtt atc acc atg gca ggc gag ctc aat att cta ccc tcc tcc   1586
Pro Asp Val Ile Thr Met Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser
510                 515                 520                 525

aca acc ccc act atc ccc tat acc att aat acg gtt gca gaa cac tta   1634
Thr Thr Pro Thr Ile Pro Tyr Thr Ile Asn Thr Val Ala Glu His Leu
                530                 535                 540

gac atg ctc atg acc tgc cac cac cta gat aaa cgc atc cgc gag gat   1682
Asp Met Leu Met Thr Cys His His Leu Asp Lys Arg Ile Arg Glu Asp
            545                 550                 555

tta caa ttt tcc caa agc cgt atc cgc ccc ggc tct atc gcc gct gaa   1730
Leu Gln Phe Ser Gln Ser Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu
        560                 565                 570

gat gtg ctc cat gat att ggc gtg atc gcg atg aca agc tcg gat tcg   1778
Asp Val Leu His Asp Ile Gly Val Ile Ala Met Thr Ser Ser Asp Ser
    575                 580                 585

caa gca atg ggg cgc gct ggc gaa gtg att cct cga act tgg cag act   1826
Gln Ala Met Gly Arg Ala Gly Glu Val Ile Pro Arg Thr Trp Gln Thr
590                 595                 600                 605

gcg gat aag aat aaa aaa gaa ttt ggt aag ctt cct gaa gat agt gca   1874
Ala Asp Lys Asn Lys Lys Glu Phe Gly Lys Leu Pro Glu Asp Ser Ala
                610                 615                 620

gat aac gac aac ttc cgt atc aaa cgc tac atc tcc aaa tac act att   1922
Asp Asn Asp Asn Phe Arg Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile
            625                 630                 635

aac ccc gct cta acc cat ggg gta agc gag tat atc ggc tct gtg gaa   1970
Asn Pro Ala Leu Thr His Gly Val Ser Glu Tyr Ile Gly Ser Val Glu
        640                 645                 650

gag ggc aaa atc gct gat ttg gtg gtg tgg aat cct gcc ttt ttt ggt   2018
Glu Gly Lys Ile Ala Asp Leu Val Val Trp Asn Pro Ala Phe Phe Gly
    655                 660                 665

gtg aaa cct aag att gtg atc aaa ggc ggt atg gtg gtc ttc tct gaa   2066
Val Lys Pro Lys Ile Val Ile Lys Gly Gly Met Val Val Phe Ser Glu
670                 675                 680                 685

atg ggc gac tcc aac gcg tcc gtg cct aca cct cag ccg gtt tat tac   2114
Met Gly Asp Ser Asn Ala Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr
                690                 695                 700
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cgc gaa atg ttt ggg cat cac ggc aag gcg aaa ttt gac acc agc atc   2162
Arg Glu Met Phe Gly His His Gly Lys Ala Lys Phe Asp Thr Ser Ile
            705                 710                 715

act ttt gtt tcc aaa gtc gcc tat gaa aat ggc gtg aaa gaa aaa cta   2210
Thr Phe Val Ser Lys Val Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu
        720                 725                 730

ggc tta gag cgc aag gtg cta ccc gtg aaa aac tgc cgc aac atc act   2258
Gly Leu Glu Arg Lys Val Leu Pro Val Lys Asn Cys Arg Asn Ile Thr
    735                 740                 745

aag aaa gac ttc aaa ttc aac aac aag acg gcg cat atc act gtc gat   2306
Lys Lys Asp Phe Lys Phe Asn Asn Lys Thr Ala His Ile Thr Val Asp
750                 755                 760                 765

cct aaa acc ttc gag gtc ttt gta gat ggc aaa ctc tgc acc tct aaa   2354
Pro Lys Thr Phe Glu Val Phe Val Asp Gly Lys Leu Cys Thr Ser Lys
                770                 775                 780

ccc gcc tct gaa gtg cct cta gcc cag cgc tac act ttc ttc tag       2399
Pro Ala Ser Glu Val Pro Leu Ala Gln Arg Tyr Thr Phe Phe
            785                 790                 795

gcncaatg                                                         2407


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Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln
             20                  25                  30

Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
         35                  40                  45

Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe
     50                  55                  60

Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
 65                  70                  75                  80
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Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
85 90 95

Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
100 105 110

Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
115 120 125

Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
130 135 140

His Phe His Phe Phe Glu Ala Asn Lys Ala Leu Lys Phe Asp Arg Glu
145 150 155 160

Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
165 170 175

Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
180 185 190

Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
195 200 205

Glu Arg His Lys His Lys Ala Leu Glu Lys Ala Lys Ser His Gly Phe
210 215 220

Ile Lys
225

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<213> Helicobacter felis

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Gly Asp Lys Val Arg Leu Gly Asp Thr Asp Leu Trp Ala Glu Val Glu
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His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys
35 40 45

Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp Glu Asn Thr

50 55 60

Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr Thr Gly Ile
65 70 75 80

Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly
85 90 95

Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val
100 105 110

Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met Ile Ile Thr
115 120 125

Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro Gln Gln Phe
130 135 140

Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly Gly Gly Thr
145 150 155 160

Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp
165 170 175

Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val
180 185 190

Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln Leu Val Glu
195 200 205

Gln Ile Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu Asp Trp Gly
210 215 220

Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala Asp Glu Tyr
225 230 235 240

Asp Val Gln Val Cys Ile His Thr Asp Thr Val Asn Glu Ala Gly Tyr
245 250 255

Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr
260 265 270

His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met
275 280 285

Ala Gly Glu Leu Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro
290 295 300

Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys

305 310 315 320

His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser
325 330 335

Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Ile
340 345 350

Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala
355 360 365

Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys Asn Lys Lys
370 375 380

Glu Phe Gly Lys Leu Pro Glu Asp Ser Ala Asp Asn Asp Asn Phe Arg
385 390 395 400

Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His
405 410 415

Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp
420 425 430

Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val
435 440 445

Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala
450 455 460

Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His
465 470 475 480

His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Val Ser Lys Val
485 490 495

Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu Gly Leu Glu Arg Lys Val
500 505 510

Leu Pro Val Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp Phe Lys Phe
515 520 525

Asn Asn Lys Thr Ala His Ile Thr Val Asp Pro Lys Thr Phe Glu Val
530 535 540

Phe Val Asp Gly Lys Leu Cys Thr Ser Lys Pro Ala Ser Glu Val Pro
545 550 555 560

Leu Ala Gln Arg Tyr Thr Phe Phe

565

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Val Lys Leu
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aca ccc aaa gag caa gaa aag ttc ttg tta tat tat gcg ggc gaa gtg 104
Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr Ala Gly Glu Val
5 10 15

gct aga aag cgc aaa gca gag ggc tta aag ctc aac caa ccc gaa gcc 152
Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln Pro Glu Ala
20 25 30 35

att gcc tac att agt gcc cat att atg gac gag gcg cgt cgt ggc aaa 200
Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg Arg Gly Lys
40 45 50

aaa acc gtt gcg gaa ctt atg gaa gag tgt atg cac ttt ttg aaa aaa 248
Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe Leu Lys Lys
55 60 65

gac gag gtg atg ccc ggg gtg ggg aat atg gtc cct gat ttg ggc gtg 296
Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp Leu Gly Val
70 75 80

gaa gcc act ttc ccc gat ggc acc aaa ctc gta act gtg aat tgg ccc 344
Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val Asn Trp Pro
85 90 95

atc gaa cct gat gaa cac ttt aag gcg ggt gaa gtg aaa ttt ggc tgt 392
Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys Phe Gly Cys

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100                 105                 110                 115

gat aaa gac att gaa ctc aac gca ggt aag gaa gtt acc gaa cta gaa   440
Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr Glu Leu Glu
                120                 125                 130

gtt act aac gaa gga cct aaa tcc ttg cat gtg ggt agc cat ttc cac   488
Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser His Phe His
            135                 140                 145

ttc ttt gaa gcc aac aaa gca ttg aaa ttc gat cgg gaa aaa gcc tat   536
Phe Phe Glu Ala Asn Lys Ala Leu Lys Phe Asp Arg Glu Lys Ala Tyr
        150                 155                 160

ggc aaa cgc cta gat att ccc tct ggc aac aca cta cgc att ggg gca   584
Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg Ile Gly Ala
    165                 170                 175

gga caa acc cgt aaa gtg cag tta atc cct ctt ggc ggt agt aaa aaa   632
Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly Ser Lys Lys
180                 185                 190                 195

gtg att ggc atg aac ggg ctt gtg aat aat att gcg gac gaa cgc cat   680
Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp Glu Arg His
                200                 205                 210

aaa cac aaa gcg cta gac aaa gca aaa tct cac gga ttt atc aag taa   728
Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly Phe Ile Lys
            215                 220                 225

ggagactccc atg aaa atg aaa aaa caa gag tat gta aat acc tac gga    777
           Met Lys Met Lys Lys Gln Glu Tyr Val Asn Thr Tyr Gly
                   230                 235                 240

ccc acc aca ggc gat aaa gtg cgc tta gga gat acc gat ctt tgg gca   825
Pro Thr Thr Gly Asp Lys Val Arg Leu Gly Asp Thr Asp Leu Trp Ala
                245                 250                 255

gaa gta gaa cat gac tat acc acc tat ggc gaa gaa ctc aaa ttc ggt   873
Glu Val Glu His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly
            260                 265                 270

gca ggt aaa act atc cgt gag ggt atg ggt cag agc aat agc cca gat   921
Ala Gly Lys Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp
        275                 280                 285

gaa aac acc tta gat tta gtg atc acc aac gcg atg att att gac tac   969
Glu Asn Thr Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr
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    290                 295                 300

acc ggg att tac aaa gcc gac att ggc att aaa aat ggc aaa atc cat   1017
Thr Gly Ile Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His
305                 310                 315                 320

ggc att ggc aag gca gga aac aag gac atg caa gat ggc gta agc cct   1065
Gly Ile Gly Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro
                325                 330                 335

cat atg gtc gtg ggt gtg ggc aca gaa gca cta gca ggg gaa ggt atg   1113
His Met Val Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met
            340                 345                 350

att att acc gct ggg ggg atc gat tca cac acc cac ttc ctc tct cca   1161
Ile Ile Thr Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro
        355                 360                 365

caa caa ttc cct acc gct cta gcc aat ggc gtt aca aca atg ttt ggc   1209
Gln Gln Phe Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly
    370                 375                 380

ggt ggc aca ggc ccc gta gat ggc acg aat gcg act acc atc act ccg   1257
Gly Gly Thr Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro
385                 390                 395                 400

ggc aaa tgg aac ttg cac cgc atg ttg cgc gca gca gaa gag tat tct   1305
Gly Lys Trp Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser
                405                 410                 415

atg aat gtg ggc ttt ttg ggc aaa ggc aat agc tct agt aaa aaa caa   1353
Met Asn Val Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln
            420                 425                 430

ctt gta gaa caa gta gaa gcg ggc gcg att ggt ttt aaa ttg cat gaa   1401
Leu Val Glu Gln Val Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu
        435                 440                 445

gac tgg ggc aca act cca agt gcg atc gat cac tgc ttg agc gta gca   1449
Asp Trp Gly Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala
    450                 455                 460

gat gaa tac gat gtg caa gtt tgt ata cac acc gat acg gtc aat gag   1497
Asp Glu Tyr Asp Val Gln Val Cys Ile His Thr Asp Thr Val Asn Glu
465                 470                 475                 480

gca ggt tat gta gat gac acc cta aat gca atg aac ggg cgc gcc atc   1545
Ala Gly Tyr Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile
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                485                 490                 495

cat gcc tac cac att gag gga gcg ggt gga gga cac tca cct gat gtt  1593
His Ala Tyr His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val
            500                 505                 510

atc acc atg gca ggc gaa gtg aat att cta ccc tcc tcc aca acc cct  1641
Ile Thr Met Ala Gly Glu Val Asn Ile Leu Pro Ser Ser Thr Thr Pro
        515                 520                 525

act atc ccc tat acc att aat acg gtt gca gaa cac tta gac atg ctt  1689
Thr Ile Pro Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu
    530                 535                 540

atg acc tgc cac cac cta gat aaa cgc atc cgc gag gat ctc caa ttt  1737
Met Thr Cys His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe
545                 550                 555                 560

tct caa agc cgt atc cgc ccc ggc tct atc gcc gct gaa gat gtg ctc  1785
Ser Gln Ser Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu
                565                 570                 575

cat gat atc ggt gtg atc gcg atg aca agt tcc gat tcg caa gca atg  1833
His Asp Ile Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met
            580                 585                 590

ggg cgc gct ggg gaa gtg att cct aga act tgg caa act gca gac aag  1881
Gly Arg Ala Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys
        595                 600                 605

aat aaa aaa gaa ttt ggt aag ctt cct gaa gat ggt gca gat aat gac  1929
Asn Lys Lys Glu Phe Gly Lys Leu Pro Glu Asp Gly Ala Asp Asn Asp
    610                 615                 620

aac ttc cgc atc aaa cgc tat atc tcc aaa tac acc att aat ccc gct  1977
Asn Phe Arg Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala
625                 630                 635                 640

ttg acc cat ggc gtg agc gag tat atc ggc tct gtg gaa gag ggc aag  2025
Leu Thr His Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys
                645                 650                 655

atc gcc gac ttg gtg gtg tgg aat cct gcc ttt ttt ggc gta aaa ccc  2073
Ile Ala Asp Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro
            660                 665                 670

aaa atc gtg atc aaa ggc ggt atg gtg gtg ttc tct gaa atg ggc gat  2121
Lys Ile Val Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp
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        675                 680                 685

tct aat gcg tct gtg ccc act cct cag ccg gtt tat tac cgc gaa atg   2169
Ser Asn Ala Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met
    690                 695                 700

ttt ggg cat cac ggc aag gcg aaa ttt gac acc agc atc act ttt gtt   2217
Phe Gly His His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Val
705                 710                 715                 720

tcc aaa gtc gcc tat gaa aat ggt gtg aaa gaa aaa cta ggt tta gag   2265
Ser Lys Val Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu Gly Leu Glu
                725                 730                 735

cgc aag gtg ctc ccc gtg aaa aac tgc cgt aac atc acc aag aag gac   2313
Arg Lys Val Leu Pro Val Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp
            740                 745                 750

ttc aag ttc aac gac aaa act gca aaa atc acc gtc gat ccg aaa acc   2361
Phe Lys Phe Asn Asp Lys Thr Ala Lys Ile Thr Val Asp Pro Lys Thr
        755                 760                 765

ttc gag gtc ttt gta gat ggc aaa ctc tgc acc tct aaa ccc acc tct   2409
Phe Glu Val Phe Val Asp Gly Lys Leu Cys Thr Ser Lys Pro Thr Ser
    770                 775                 780

gaa gtg cct cta gcc caa cgc tac act ttc ttc tag gcataat           2452
Glu Val Pro Leu Ala Gln Arg Tyr Thr Phe Phe
785                 790                 795
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<212> PRT
<213> Helicobacter felis

<400> 14

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Val Lys Leu Thr Pro Lys Glu Gln Glu Lys Phe Leu Leu Tyr Tyr Ala
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Gly Glu Val Ala Arg Lys Arg Lys Ala Glu Gly Leu Lys Leu Asn Gln
             20                  25                  30

Pro Glu Ala Ile Ala Tyr Ile Ser Ala His Ile Met Asp Glu Ala Arg
         35                  40                  45

Arg Gly Lys Lys Thr Val Ala Glu Leu Met Glu Glu Cys Met His Phe
     50                  55                  60
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Leu Lys Lys Asp Glu Val Met Pro Gly Val Gly Asn Met Val Pro Asp
65 70 75 80

Leu Gly Val Glu Ala Thr Phe Pro Asp Gly Thr Lys Leu Val Thr Val
85 90 95

Asn Trp Pro Ile Glu Pro Asp Glu His Phe Lys Ala Gly Glu Val Lys
100 105 110

Phe Gly Cys Asp Lys Asp Ile Glu Leu Asn Ala Gly Lys Glu Val Thr
115 120 125

Glu Leu Glu Val Thr Asn Glu Gly Pro Lys Ser Leu His Val Gly Ser
130 135 140

His Phe His Phe Phe Glu Ala Asn Lys Ala Leu Lys Phe Asp Arg Glu
145 150 155 160

Lys Ala Tyr Gly Lys Arg Leu Asp Ile Pro Ser Gly Asn Thr Leu Arg
165 170 175

Ile Gly Ala Gly Gln Thr Arg Lys Val Gln Leu Ile Pro Leu Gly Gly
180 185 190

Ser Lys Lys Val Ile Gly Met Asn Gly Leu Val Asn Asn Ile Ala Asp
195 200 205

Glu Arg His Lys His Lys Ala Leu Asp Lys Ala Lys Ser His Gly Phe
210 215 220

Ile Lys
225

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His Asp Tyr Thr Thr Tyr Gly Glu Glu Leu Lys Phe Gly Ala Gly Lys

35 40 45

Thr Ile Arg Glu Gly Met Gly Gln Ser Asn Ser Pro Asp Glu Asn Thr
50 55 60

Leu Asp Leu Val Ile Thr Asn Ala Met Ile Ile Asp Tyr Thr Gly Ile
65 70 75 80

Tyr Lys Ala Asp Ile Gly Ile Lys Asn Gly Lys Ile His Gly Ile Gly
85 90 95

Lys Ala Gly Asn Lys Asp Met Gln Asp Gly Val Ser Pro His Met Val
100 105 110

Val Gly Val Gly Thr Glu Ala Leu Ala Gly Glu Gly Met Ile Ile Thr
115 120 125

Ala Gly Gly Ile Asp Ser His Thr His Phe Leu Ser Pro Gln Gln Phe
130 135 140

Pro Thr Ala Leu Ala Asn Gly Val Thr Thr Met Phe Gly Gly Gly Thr
145 150 155 160

Gly Pro Val Asp Gly Thr Asn Ala Thr Thr Ile Thr Pro Gly Lys Trp
165 170 175

Asn Leu His Arg Met Leu Arg Ala Ala Glu Glu Tyr Ser Met Asn Val
180 185 190

Gly Phe Leu Gly Lys Gly Asn Ser Ser Ser Lys Lys Gln Leu Val Glu
195 200 205

Gln Val Glu Ala Gly Ala Ile Gly Phe Lys Leu His Glu Asp Trp Gly
210 215 220

Thr Thr Pro Ser Ala Ile Asp His Cys Leu Ser Val Ala Asp Glu Tyr
225 230 235 240

Asp Val Gln Val Cys Ile His Thr Asp Thr Val Asn Glu Ala Gly Tyr
245 250 255

Val Asp Asp Thr Leu Asn Ala Met Asn Gly Arg Ala Ile His Ala Tyr
260 265 270

His Ile Glu Gly Ala Gly Gly Gly His Ser Pro Asp Val Ile Thr Met
275 280 285

Ala Gly Glu Val Asn Ile Leu Pro Ser Ser Thr Thr Pro Thr Ile Pro

290 295 300

Tyr Thr Ile Asn Thr Val Ala Glu His Leu Asp Met Leu Met Thr Cys
305 310 315 320

His His Leu Asp Lys Arg Ile Arg Glu Asp Leu Gln Phe Ser Gln Ser
325 330 335

Arg Ile Arg Pro Gly Ser Ile Ala Ala Glu Asp Val Leu His Asp Ile
340 345 350

Gly Val Ile Ala Met Thr Ser Ser Asp Ser Gln Ala Met Gly Arg Ala
355 360 365

Gly Glu Val Ile Pro Arg Thr Trp Gln Thr Ala Asp Lys Asn Lys Lys
370 375 380

Glu Phe Gly Lys Leu Pro Glu Asp Gly Ala Asp Asn Asp Asn Phe Arg
385 390 395 400

Ile Lys Arg Tyr Ile Ser Lys Tyr Thr Ile Asn Pro Ala Leu Thr His
405 410 415

Gly Val Ser Glu Tyr Ile Gly Ser Val Glu Glu Gly Lys Ile Ala Asp
420 425 430

Leu Val Val Trp Asn Pro Ala Phe Phe Gly Val Lys Pro Lys Ile Val
435 440 445

Ile Lys Gly Gly Met Val Val Phe Ser Glu Met Gly Asp Ser Asn Ala
450 455 460

Ser Val Pro Thr Pro Gln Pro Val Tyr Tyr Arg Glu Met Phe Gly His
465 470 475 480

His Gly Lys Ala Lys Phe Asp Thr Ser Ile Thr Phe Val Ser Lys Val
485 490 495

Ala Tyr Glu Asn Gly Val Lys Glu Lys Leu Gly Leu Glu Arg Lys Val
500 505 510

Leu Pro Val Lys Asn Cys Arg Asn Ile Thr Lys Lys Asp Phe Lys Phe
515 520 525

Asn Asp Lys Thr Ala Lys Ile Thr Val Asp Pro Lys Thr Phe Glu Val
530 535 540

Phe Val Asp Gly Lys Leu Cys Thr Ser Lys Pro Thr Ser Glu Val Pro

545 550 555 560

Leu Ala Gln Arg Tyr Thr Phe Phe
565